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Signed R. Mahoney

Dated 28 July 2003

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1/77

16JUL02 E733436-1 D02934
P01/7700 0.00-0216375.6

Request for grant of a patent

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16JUL02 E733436-1 D02934
P01/7700 0.00-0216379.8

1. Your reference — 100756

2. Patent application number *(The Patent Office will fill in this part)* — 13 JUL 2002 — 0216379.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 07822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention — COMPOUNDS

5. Name of your agent *(if you have one)* — Margareta Linderoth

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 08425308001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	56
Claim(s)	04
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 12/07/2002

12. Name and daytime telephone number of person to contact in the United Kingdom — Jennifer C Bennett - 01625 230148

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COMPOUNDS

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes and are particularly effective as inhibitors of TNF (Tumour Necrosis Factor). Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMP) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biologically important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many disease conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these disease conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis),

inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease)); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis.

A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting TACE. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

TACE (also known as ADAM17) which has been isolated and cloned [R.A. Black *et al.* (1997) Nature 385:729-733; M.L. Moss *et al.* (1997) Nature 385:733-736] is a member of the admalysin family of metalloproteins. TACE has been shown to be responsible for the cleavage of pro-TNFα, a 26kDa membrane bound protein to release 17kDa biologically active soluble TNFα. [Schlondorff *et al.* (2000) Biochem. J. 347: 131-138]. TACE mRNA is found in most tissues, however TNFα is produced primarily by activated monocytes, macrophages and T lymphocytes. TNFα has been implicated in a wide range of pro-inflammatory biological processes including induction of adhesion molecules and chemokines to promote cell trafficking, induction of matrix destroying enzymes, activation of fibroblasts to produce prostaglandins and activation of the immune system [Aggarwal *et al* (1996) Eur. Cytokine Netw. 7: 93-124]. Clinical use of the anti-TNF biologicals has shown TNFα to play an important role in a range of inflammatory diseases including rheumatoid arthritis, Crohn's disease and psoriasis [Onrust *et al* (1998) Biodrugs 10: 397-422, Jarvis et al (1999) Drugs 57:945-964]. TACE activity has also been implicated in the shedding of other membrane bound proteins including TGFα, p75 & p55 TNF receptors, L-selectin and amyloid precursor protein [Black (2002) Int. J. Biochem. Cell Biol. 34: 1-5]. The biology of TACE inhibition has recently been reviewed and shows TACE to have a central role in TNFα production and selective TACE inhibitors to have equal, and possibly greater, efficacy in the collagen

induced arthritis model of RA than strategies that directly neutralise TNFα [Newton et al (2001) Ann. Rheum. Dis. 60: iii25-iii32].

A TACE inhibitor might therefore be expected to show efficacy in all disease where TNFα has been implicated including, but not limited to, inflammatory diseases including rheumatoid arthritis and psoriasis, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy.

WO 99/24399 discloses compounds that are useful as therapeutic agents by virtue of having MMP and TNF inhibitory activity.

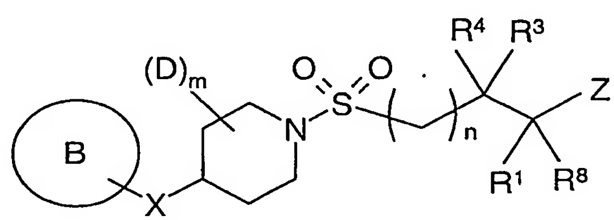
WO 99/38843 discloses compounds useful in the treatment of cancer, inflammation and other conditions associated with matrix metalloproteinases or that are mediated by TNF α or enzymes involved in the shedding of *L*-selectin, CD23, the TNF receptors, IL-1 receptors or IL-6 receptors.

EP 1109787 discloses compounds useful in the inhibition of metalloproteinases. These compounds are of particular interest in inhibiting MMP-13 as well as MMP-9.

Surprisingly we have discovered that a selection of compounds are very potent inhibitors of TACE (ADAM17) and are particularly noteworthy for their unexpected selectivity for TACE over the matrix metalloproteinases

Additionally further effective compounds are disclosed.

According to one aspect of the present invention there is provided compounds of the formula (1):



formula (1)

wherein Z is selected from $-CONR^{15}OH$ and $-N(OH)CHO$;

R^{15} is hydrogen or C_{1-3}alkyl;

wherein R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$;

R^{16} is hydrogen or C_{1-3}alkyl;

R^{17} is selected from halo, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy;

R^2 is group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^6 is hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^5 and R^6 together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

wherein R^8 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy and C_{1-4}alkyl;

or R^1 and R^8 together form a carbocyclic or saturated heterocyclic 3- to 6-membered ring;

wherein R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocyclyl, aryl or heteroaryl;

wherein n is 0 or 1;

wherein m is 0 or 1;

wherein D is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl or fluoro;

wherein X is $-(CR^9R^{10})_t-Q-(CR^{11}R^{12})_u-$ where t and u are independently 0 or 1 with the proviso that t and u cannot both be 0;

wherein Q is O, S, SO or SO_2;

R^9, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

wherein B is a group selected from aryl, heteroaryl, heterocyclyl, C_{3-10}cycloalkyl and C_{5-7}cycloalkenyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethyloxy, halo, C_{1-4}alkyl (optionally substituted by one or more R^{13}), C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{13}), heterocycloalkyl, heteroaryl, $-OR^{13}$, cyano, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{16}COR^{13}$, $-SO_2NR^{13}R^{14}$, $-NR^{16}SO_2R^{13}$, $-SR^{13}$, $-SOR^7$ and $-SO_2R^7$;

R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl

R^{13} and R^{14} are independently hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^{13} and R^{14} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring.

In another aspect, the invention relates to compounds of formula **(1)** as hereinabove defined or to a pharmaceutically acceptable salt thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses metalloproteinases inhibition activity and in particular TACE inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Compounds of formula (1) are therefore provided as enatiomers, diastereomers, geometric isomers and atropisomers.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has metalloproteinases inhibition activity and in particular TACE inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have metalloproteinases inhibition activity and in particular TACE inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess metalloproteinases inhibition activity and in particular TACE inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such

salts. Such acid addition salts include but are not limited to hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where the compounds of formula (1) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine or tris-(2-hydroxyethyl)amine.

The compounds of formula (1) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example, $R^AC(O)O(C_{1-6})$alkyl-

CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_{1-4})alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "C_{1-3}alkyl" includes methyl, ethyl, propyl and isopropyl, examples of "C_{1-4}alkyl" include the examples of "C_{1-3}alkyl", butyl and *t*-butyl and examples of "C_{1-6}alkyl" include the examples of "C_{1-4}alkyl"and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. Examples of "C_{1-20}alkyl" include the examples of "C_{1-6}alkyl" and other straight-chain and branched chain alkyl groups. An analogous convention applies to other generic terms, for example "C_{2-4}alkenyl" includes vinyl, allyl and 1-propenyl and examples of "C_{2-6}alkenyl" include the examples of "C_{2-4}alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "C_{2-4}alkynyl" includes ethynyl, 1-propynyl and 2-propynyl and examples of "C_{2-6}alkynyl"include the examples of "C_{2-4}alkynyl" and additionally 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

The term "C_{3-6}cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "C_{3-7}cycloalkyl" includes "C_{3-6}cycloalkyl" and additionally cycloheptyl. The term "C_{3-10}cycloalkyl" includes "C_{3-7}cycloalkyl" and additionally cyclooctyl, cyclononyl and cyclodecyl.

"Heterocycloalkyl" is a monocyclic saturated 3- to 10-membered ring containing 1 or 2 heteroatoms selected from nitrogen, sulphur and oxygen wherein a ring nitrogen or sulphur may be oxidised to the N-oxide or S-oxide(s).

"C_{5-7}cycloalkenyl" is a monocyclic 5 to 7-membered ring containing 1, 2 or 3 double bonds. Examples are cyclopentenyl and cyclohexenyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C_{1-4}alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "C_{1-6}alkoxy" include the examples of "C_{1-4}alkoxy" and additionally pentyloxy, 1-ethylpropoxy and hexyloxy. Examples of "C_{1-4}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and isopropoxycarbonyl .

Examples of "aryl" are phenyl and naphthyl.

Examples of "arylC_{1-4}alkyl" are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

"Heteroaryl" is monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen may be oxidised. Examples of heteroaryl are pyridyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl and pyrazinyl. Preferably heteroaryl is pyridyl, imidazolyl, quinolinyl, pyrimidinyl, thienyl, pyrazolyl, thiazolyl, oxazolyl and isoxazolyl.

Examples of "heteroarylC_{1-4}alkyl" are pyridylmethyl, pyridylethyl, pyrimidinylethyl, pyrimidinylpropyl, quinolinylpropyl and oxazolylmethyl.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring containing 4 to 12 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-; a ring nitrogen or sulphur atom may be optionally oxidised to form the N-oxide or S-oxide(s); and a –NH group may be optionally substituted by acetyl, formyl, methyl or mesyl. Examples and suitable values of the term "heterocyclyl" are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, piperazinyl, *N*-formypiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, pyranyl, dihydro-*2H*-pyranyl, tetrahydrofuranyl, 2,2-dimethyl-1,3-dioxolanyl and 3,4-dimethylenedioxybenzyl. Preferred values are 3,4-dihydro-*2H*-pyran-5-yl, tetrahydrofuran-2-yl, 2,2-dimethyl-1,3-dioxolan-2-yl and 3,4-dimethylenedioxybenzyl.

Heterocyclic rings are rings containing 1, 2 or 3 rings atoms selected nitrogen, oxygen and sulphur. "Heterocyclic 5 to 7-membered" rings are pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl, thiomorpholinyl , thiopyranyl and morpholinyl. "Heterocyclic 4 to 7-membered" rings include the examples of "heterocyclic 5 to 7-membered" and additionally azetidinyl.

"Saturated heterocyclic 3 to 7-membered" rings are oxiranyl, aziridinyl, thiirane, azetidinyl, oxetanyl, thietanyl, tetrahydrothienyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydro-2H-thiopyranyl and piperidinyl and a ring nitrogen may be substituted by a group selected from formyl, acetyl and mesyl.

A "carbocyclic 3 to 6-membered" ring is a saturated, partially saturated or unsaturated ring containing 3 to 6 ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopent-3-enyl, cyclohexyl and cyclopent-2-enyl.

Where optional substituents are chosen from "one of more" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. Preferably "one or more" means "1, 2 or 3" and this is particularly the case when the group or substituent is halo. "One or more" may also means "1 or 2".

Compounds of the present invention have been occasionally been named with the aid of computer software (ACD/Name version 5.09).

Preferred values of Z, R^1, R^3, R^4, R^8, n, m, D, X and B are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein Z is $-CONR^{15}OH$.

In another aspect of the invention Z is $-N(OH)CHO$.

In one aspect of the invention R^{15} is hydrogen, methyl, ethyl or isopropyl.

In another aspect R^{15} is hydrogen.

In one aspect of the invention R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-6}cycloalkyl (optionally substituted by R^{17}), aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$.

In another aspect of the invention R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$ and $-NR^{16}COR^5$.

In another aspect R^1 is hydrogen or a group selected from methyl, ethyl, propyl, isopropyl, t-butyl, 2-methylpropyl, ethynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, pyridyl, thienyl, pyrimidinyl, quinolinyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, piperidinyl, 3,4-dimethylenedioxybenzyl, 3,4-dihydro-2*H*-pyran-5-yl, tetrahydrofuran-2-yl and 2,2-dimethyl-1,3-dioxolan-2-yl where the group is optionally substituted by one or more substituents independently selected from fluoro, chloro, bromo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, methyl, ethyl, C_{2-4}alkenyl, C_{3-6}cycloalkyl (optionally substituted by R^{17}), phenyl (optionally substituted by R^{17}), pyrimidinyl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$.

In another aspect R^1 is selected from hydrogen, methyl, ethyl, propyl, isopropyl, t-butyl, 2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyloxymethyl, phenyl, benzyl, phenethyl, phenylpropyl, (5-fluoropyrimidin-2-yl)ethyl, (5-fluoropyrimidin-2-yl)propyl, pyrimindin-2-ylethyl, pyrimidin-2-ylpropyl, naphth-2-yl, naphth-1-yl, 3,4-dichlorophenyl, 4-chlorophenyl, biphenylyl, 3-nitrophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-bromophenyl, 4-(methoxycarbonyl)phenyl, 4-benzyloxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-(4-chlorophenoxy)phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-bromothien-5-yl, 2-methylthien-5-yl, pyrimidin-2-yl, 2-methylpyrimidin-5-yl, 2-methylpyrimidin-4-yl, quinolin-4-yl, 3,4-methylenedioxybenzyl, ethynyl, methoxymethyl, 3,4-dihydro-2*H*-pyran-5-yl, tetrahydrofuran-2-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, thiazol-2-yl, oxazol-2-yl, isoxazol-5-yl, isoxazol-3-yl, 4,4-difluorocyclohexyl, pyrimidin-2-ylmethyl, 2-pyrimidin-2-ylethyl, 3-pyrimidin-2-ylpropyl, 2,2,2-trifluoroethyl, *N*-acetylpiperidin-4-yl, *N*-methanesulfonylpiperidin-4-yl, 3-bromo-4-hydroxyphenyl, 4-fluoro-2-trifluoromethylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 6-methylpyrid-2-yl, 2-methylpyrid-2-yl, 5-cyanoindol-yl, pyrimidin-5-yl, imidazol-4-yl, 1*H*-imidazol-4-yl, pyrazol-3-yl, 1*H*-pyrazol-3-yl and (*N*-acetylamino)phenyl.

In a further aspect of the invention, R^1 is phenyl, 4-fluorophenyl, 3-pyrimidin-2-ylpropyl, 3-bromo-4-hydroxyphenyl, 3-trifluoromethylphenyl, pyrid-3-yl, methyl, imidazol-4-yl, pyrazol-3-yl and (*N*-acetylamino)phenyl.

In one aspect of the invention R^{16} is hydrogen, methyl or ethyl.

In another aspect R^{16} is methyl or ethyl.

In another aspect of the invention R^{16} is hydrogen.

In one aspect of the invention R^{17} is halo or C_{1-4}alkyl.

In another aspect R^{17} is fluoro, chloro, bromo or methyl.

In another aspect of the invention R^{17} is fluoro or methyl.

In one aspect of the invention R^2 is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo.

In another aspect R^2 is a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R^2 is methyl.

In one aspect of the invention R^5 is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo.

In another aspect R^5 is hydrogen or a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R^6 is hydrogen, methyl, ethyl, propyl or isopropyl.

In one aspect of the invention R^8 is hydrogen, methyl, ethyl, propyl or isopropyl.

In another aspect R^8 is hydrogen.

In one aspect of the invention R^3 is hydrogen, methyl, ethyl or phenyl.

In another aspect R^3 is hydrogen.

In one aspect of the invention R^4 is hydrogen, methyl, ethyl or phenyl.

In another aspect R^4 is hydrogen.

In one aspect of the invention n is 0.

In another aspect n is 1.

In one aspect of the invention m is 0.

In another aspect of the invention m is 1.

In one aspect of the invention D is hydrogen, methyl or fluoro.

In another aspect D is hydrogen.

In one aspect of the invention X is $-CR^9R^{10}-Q-$, $-Q-CR^{11}R^{12}-$ or $-CR^9R^{10}-Q-CR^{11}R^{12}-$.

In another aspect of the invention X is $-(CH_2)-Q-$, $-Q-(CH_2)-$ or $-(CH_2)-Q-(CH_2)-$ or $-(CHMe)-Q-$.

In a further aspect of the invention X is $-(CH_2)-O-$, $-O-(CH_2)-$ or $-(CH_2)-O-(CH_2)-$ or $-(CHMe)-O-$.

In one aspect of the invention Q is O.

In one aspect of the invention t is 1.

In another aspect t is 0, provided that u is not 0.

In one aspect of the invention u is 1.

In another aspect u is 0, provided that t is not 0.

In one aspect of the invention R^9 is hydrogen or methyl.

In one aspect of the invention R^{10} is hydrogen.

In one aspect of the invention R^{11} is hydrogen.

In one aspect of the invention R^{12} is hydrogen.

In one aspect of the invention B is a group selected from aryl, heteroaryl, heterocyclyl, C_{3-10}cycloalkyl, and C_{5-7}cycloalkenyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, halo, C_{1-4}alkyl, heteroaryl, $-OR^{13}$, cyano, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$ and $-NR^{16}COR^{13}$.

In another aspect B is phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, thieno[2,3-b]pyridyl, thieno[3,2-b]pyridyl, 1,8-naphthyridinyl, cyclohexyl, 3,4-methylenedioxybenzyl

where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethyloxy, halo, C_{1-4}alkyl (optionally substituted by one or more R^{13}), C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{13}), heteroaryl, $-OR^{13}$, cyano, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{16}COR^{13}$, $-SO_2NR^{13}R^{14}$, $-NR^{16}SO_2R^{13}$, $-SR^{13}$, $-SOR^7$ and $-SO_2R$.

In another aspect B is phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, thieno[2,3-b]pyridyl, thieno[3,2-b]pyridyl, 1,8-naphthyridinyl, cyclohexyl, 3,4-methylenedioxybenzyl where each group is optionally substituted by one or more groups independently selected from trifluoromethyl, fluoro, chloro, bromo, methyl, isopropyl or cyano.

In another aspect B is quinolin-4-yl, naphthyl, 2-methylquinolin-4-yl, 3-methylnaphthyl, 7-methylquinolin-5-yl, 6-methylquinolin-8-yl, 7-methylisoquinolin-5-yl, 6-methylthieno[2,3-b]pyridyl, 5-methylthieno[3,2-b]pyridyl, 2-methyl-1,8-naphthyridinyl, 2-trifluoromethylquinolin-4-yl, 2-ethynylquinolin-4-yl, 7-chloroquinolin-5-yl, 7-fluoro-2-methylquinolin-4-yl, 2-methyl-*N*-oxoquinolin-4-yl, 3-methylisoquinolin-1-yl, 5-fluoro-2-methylquinolin-4-yl, 2,6-dimethylpyrid-4-yl, 2,5-dimethylpyridin-4-yl, 2,5-dimethylphenyl, 3-methoxyphenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2,6-difluoro-3-methylphenyl, 2-chloro-6-fluorophenyl, 3-fluoro-6-methylphenyl, phenyl, 2-methylphenyl, 3-chlorophenyl, 2-bromophenyl, 2-fluorophenyl, 2,6-difluorophenyl, 3-fluorophenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 4-chlorophenyl, cyclohexyl, 4-bromophenyl, 2-cyanophenyl, 4-fluorophenyl, 2-fluoro-3-methylphenyl, 4-methylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,4,6-trimethylphenyl, 3-methylphenyl, 3,4-dimethylphenyl, 4-methoxyphenyl, 3,5-dimethylphenyl, 4-prop-2-ylphenyl, 3-chloro-4-methylphenyl, 3,4-methylenedioxybenzyl, 5-fluoro-2-methylpyridinyl, 2,4-dimethylphenyl or 1-methylquinolinyl.

In a further aspect, B is 2,5-difluorophenyl, 2,5-dimethylphenyl, 2-cyanophenyl, 2-methylquinolin-4-yl or 2,5-dimethylpyrid-4-yl.

In one aspect of the invention R^7 is C_{1-4}alkyl.

In another aspect R^7 is methyl, ethyl, propyl or isopropyl.

In one aspect of the invention R^{13} is hydrogen or C_{1-4}alkyl.

In another aspect R^{13} is methyl.

In one aspect of the invention R^{14} is hydrogen or C_{1-4}alkyl.

In another aspect R^{14} is hydrogen or methyl.

In a further aspect R^{13} and R^{14} together with the nitrogen to which they are attached form a heterocyclic 5 to 7-membered ring.

A preferred class of compound is of the formula (1) wherein;

Z is –N(OH)CHO;

R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$ and $-NR^{16}COR^5$;

R^{16} is hydrogen, methyl or ethyl;

R^{17} is halo or C_{1-4}alkyl;

R^2 is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^6 is hydrogen, methyl, ethyl, propyl or isopropyl;

R^8 is hydrogen, methyl, ethyl, propyl or isopropyl;

R^3 is hydrogen, methyl, ethyl or phenyl;

R^4 is hydrogen, methyl, ethyl or phenyl;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$, $-O-(CH_2)-$ or $-(CH_2)-O-(CH_2)-$ or $-(CHMe)-O-$;

B is a group selected from aryl, heteroaryl, heterocyclyl and C_{3-10}cycloalkyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, halo, C_{1-4}alkyl, heteroaryl, $-OR^{13}$, cyano, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$ and $-NR^{16}COR^{13}$;

R^7 is C_{1-4}alkyl;

R^{13} is hydrogen or C_{1-4}alkyl; and

R^{14} is hydrogen or C_{1-4}alkyl.

Another preferred class of compounds are of formula (1) wherein:

Z is $-CONR^{15}OH$;

R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$ and $-NR^{16}COR^5$;

R^{15} is hydrogen, methyl, ethyl or isopropyl;

R^{16} is hydrogen;

R^{17} is halo or C_{1-4}alkyl;

R^2 is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo;

R^6 is hydrogen, methyl, ethyl, propyl or isopropyl;

R^8 is hydrogen, methyl, ethyl, propyl or isopropyl;

R^3 is hydrogen, methyl, ethyl or phenyl;

R^4 is hydrogen, methyl, ethyl or phenyl;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$, $-O-(CH_2)-$ or $-(CH_2)-O-(CH_2)-$ or $-(CHMe)-O-$;

B is a group selected from aryl, heteroaryl, heterocyclyl and C_{3-10}cycloalkyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, halo, C_{1-4}alkyl, heteroaryl, $-OR^{13}$, cyano, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$ and $-NR^{16}COR^{13}$;

R^7 is C_{1-4}alkyl;

R^{13} is hydrogen or C_{1-4}alkyl; and

R^{14} is hydrogen or C_{1-4}alkyl.

A further preferred class of compounds are of formula (1) wherein:

Z is –N(OH)CHO;

R^1 is selected from hydrogen, methyl, ethyl, propyl, isopropyl, t-butyl, 2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, benzyloxymethyl, phenyl, benzyl, phenethyl, phenylpropyl, (5-fluoropyrimidin-2-yl)ethyl, (5-fluoropyrimidin-2-yl)propyl, pyrimidin-2-ylethyl, pyrimidin-2-ylpropyl, naphth-2-yl, naphth-1-yl, 3,4-dichlorophenyl, 4-chlorophenyl, biphenylyl, 3-nitrophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-bromophenyl, 4-(methoxycarbonyl)phenyl, 4-benzyloxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-(4-chlorophenoxy)phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-bromothien-5-yl, 2-methylthien-5-yl, pyrimidin-2-yl, 2-methylpyrimidin-5-yl, 2-methylpyrimidin-4-yl, quinolin-4-yl, 3,4-methylenedioxybenzyl, ethynyl, methoxymethyl, 3,4-dihydro-2*H*-pyran-5-yl, tetrahydrofuran-2-yl, 2,2-dimethyl-1,3-dioxolan-4-yl, thiazol-2-yl, oxazol-2-yl, isoxazol-5-yl, isoxazol-3-yl 4,4-difluorocyclohexyl, pyrimidin-2-ylmethyl, 2-pyrimidin-2-ylethyl, 3-pyrimidin-2-ylpropyl, 2,2,2-trifluoroethyl, *N*-acetylpiperidin-4-yl, *N*-methanesulfonylpiperidin-4-yl, 3-bromo-4-hydroxyphenyl, 4-fluoro-2-trifluoromethylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 6-methylpyrid-2-yl, 2-methylpyrid-2-yl, 5-cyanoindol-yl, pyrimidin-5-yl,imidazol-4-yl, pyrazol-3-yl, 1*H*-imidazol-4-yl, 1*H*-pyrazol-3-yl and (*N*-acetylamino)phenyl;

R^8 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

X is $-(CH_2)-O-$, $-O-(CH_2)-$ or $-(CH_2)-O-(CH_2)-$ or $-(CHMe)-O-$; and

B is quinolin-4-yl, naphthyl, 2-methylquinolin-4-yl, 3-methylnaphthyl, 7-methylquinolin-5-yl, 6-methylquinolin-8-yl, 7-methylisoquinolin-5-yl, 6-methylthieno[2,3-b]pyridyl, 5-methylthieno[3,2-b]pyridyl, 2-methyl-1,8-naphthyridinyl, 2-trifluoromethylquinolin-4-yl, 2-ethynylquinolin-4-yl, 7-chloroquinolin-5-yl, 7-fluoro-2-methylquinolin-4-yl, 2-methyl-*N*-oxoquinolin-4-yl, 3-methylisoquinolin-1-yl, 5-fluoro-2-methylquinolin-4-yl, 2,6-dimethylpyrid-4-yl, 2,5-dimethylpyridin-4-yl, 2,5-dimethylphenyl, 3-methoxyphenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2,6-difluoro-3-methylphenyl, 2-chloro-6-fluorophenyl, 3-fluoro-6-methylphenyl, phenyl, 2-

methylphenyl, 3-chlorophenyl, 2-bromophenyl, 2-fluorophenyl, 2,6-difluorophenyl, 3-fluorophenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 4-chlorophenyl, cyclohexyl, 4-bromophenyl, 2-cyanophenyl, 4-fluorophenyl, 2-fluoro-3-methylphenyl, 4-methylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,4,6-trimethylphenyl, 3-methylphenyl, 3,4-dimethylphenyl, 4-methoxyphenyl, 3,5-dimethylphenyl, 4-prop-2-ylphenyl, 3-chloro-4-methylphenyl, 3,4-methylenedioxybenzyl, 5-fluoro-2-methylpyridinyl, 2,4-dimethylphenyl or 1-methylquinolinyl.

In another aspect of the invention, preferred compounds of the invention are any one of:

1-[({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl]-3-phenylpropyl(hydroxy)formamide;

2-({4-[(3-methoxybenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2,5-difluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(3,5-difluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

1-phenyl-2-{[4-(pyridin-2-ylmethoxy)piperidin-1-yl]sulfonyl}ethyl(hydroxy)formamide;

1-phenyl-2-{[4-(pyridin-3-ylmethoxy)piperidin-1-yl]sulfonyl}ethyl(hydroxy)formamide;

2-({4-[(2,6-difluoro-3-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2-chloro-6-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(5-fluoro-2-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-{[4-(benzyloxy)piperidin-1-yl]sulfonyl}-1-phenylethyl(hydroxy)formamide;

2-({4-[(2-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(3-chlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2-bromobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2,6-difluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(3-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(4-trifluoromethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2-chlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(3,4-dichlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(4-chlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-{[4-(cyclohexylmethoxy)piperidin-1-yl]sulfonyl}-1-phenylethyl(hydroxy)formamide;

2-{[4-(2-naphthylmethoxy)piperidin-1-yl]sulfonyl}-1-phenylethyl(hydroxy)formamide;

2-({4-[(4-bromobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

2-({4-[(2,5-dimethylphenoxy)methyl]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethyl(hydroxy)formamide;

1-benzyl-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;

2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethyl(hydroxy)formamide;

2-({4-[(4-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

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2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

1-phenyl-2-{[4-(pyridin-4-ylmethoxy)piperidin-1-yl]sulfonyl}ethyl(hydroxy)formamide;

2-({4-[(2-fluoro-3-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

1-({[4-(benzyloxy)piperidin-1-yl]sulfonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-methylethyl(hydroxy)formamide;

1-(3-bromo-4-hydroxyphenyl)-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;

2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-[4-fluoro-2-(trifluoromethyl)phenyl]ethyl(hydroxy)formamide;

2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-[2-(trifluoromethyl)phenyl]ethyl(hydroxy)formamide;

2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-[3-(trifluoromethyl)phenyl]ethyl(hydroxy)formamide;

2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

1-[({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)-1-phenylethyl(hydroxy)formamide;

1-methyl-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;

1-[({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

1-{[(4-{[(2,5-dimethylbenzyl)oxy]methyl}piperidin-1-yl)sulfonyl]methyl}-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

1-(1*H*-imidazol-4-yl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;

2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)-1-(1*H*-pyrazol-3-yl)ethyl(hydroxy)formamide;

2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)-1-(4-acetamidophenyl)ethyl(hydroxy)formamide;

3-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-*N*-hydroxy-2-phenylpropanamide;

1-[({4-[(2,6-dimethylpyridin-4-yl)methoxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

2-{[4-(1-phenylethoxy)piperidin-1-yl]sulfonyl}-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(4-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2-chlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2,4-dichlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2-chloro-5-fluorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2,6-dichlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(2,4,6-trimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3-chlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3,4-dichlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3-methoxybenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3-methybenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3,4-dimethybenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(4-chlorobenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(4-methoxybenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3,5-dimethybenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(4-isopropylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-({4-[(3-chloro-4-methylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide;

2-{[4-(1,3-benzodioxol-5-ylmethoxy)piperidin-1-yl]sulfonyl}-1-pyridin-3-ylethyl(hydroxy)formamide;

1-[({4-[(2,5-dimethylpyridin-4-yl)methoxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

3-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-phenylpropyl(hydroxy)formamide;

1-{[(4-{[(2-methylquinolin-4-yl)methoxy]methyl}piperidin-1-yl)sulfonyl]methyl}-4-pyrimidin-2-ylbutyl(hydroxy)formamide;

1-[({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)methyl]propyl(hydroxy)formamide;

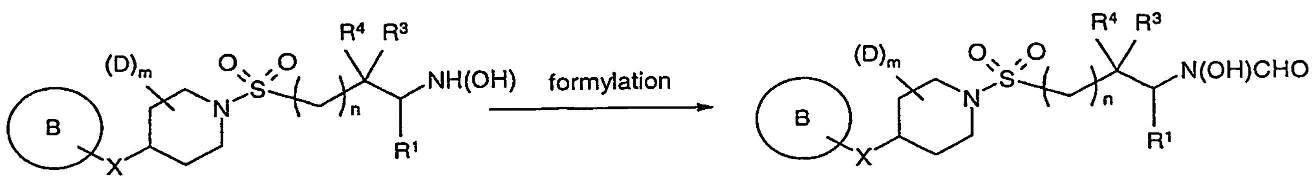
2-methyl-1-[({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)methyl]propyl(hydroxy)formamide;

3-methyl-1-[({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)methyl]butyl(hydroxy)formamide;

1-cyclopropyl-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;
1-(3-fluorophenyl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;
1-(4-fluorophenyl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide;
1-(3-trifluoromethylphenyl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide; and
1-(4-trifluoromethylphenyl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof wherein Z is –N(OH)CHO, which process comprises the steps of:

a) converting a hydroxylamine of formula (2) into a compound of formula (1);



Scheme 1

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

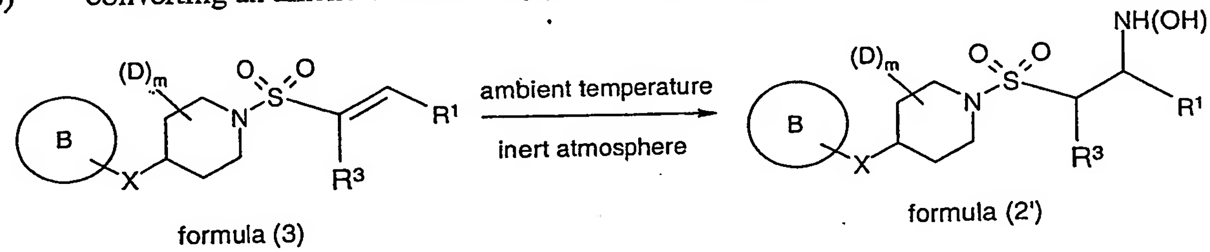
iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Formylation may be suitably performed by adding a preformed mixture of acetic acid (8 equivalents) and formic acid (excess) to formula (2) in THF or DCM and stirring the solution for 15h at temperatures ranging from 0°C to room temperature followed by stirring in methanol. Alternatively a formylation method described in *J.Med.Chem.*, 2002, *45*, 219 using trifluoroethylformate can be used.

This process may further comprise a process for the preparation of a hydroxylamine of formula (2):

- when n is 0 and R^4 is hydrogen (indicated as a compound of formula (2')),which process comprises:

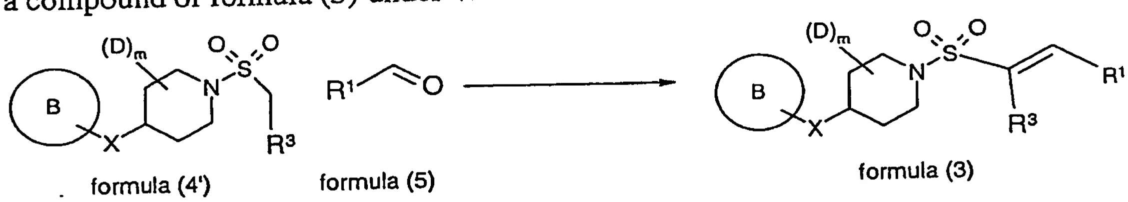
b) converting an alkene of formula (3) into a hydroxylamine of formula (2') ;



Scheme 2

Suitable reagents for such a conversion include aqueous hydroxylamine in THF under an argon atmosphere.

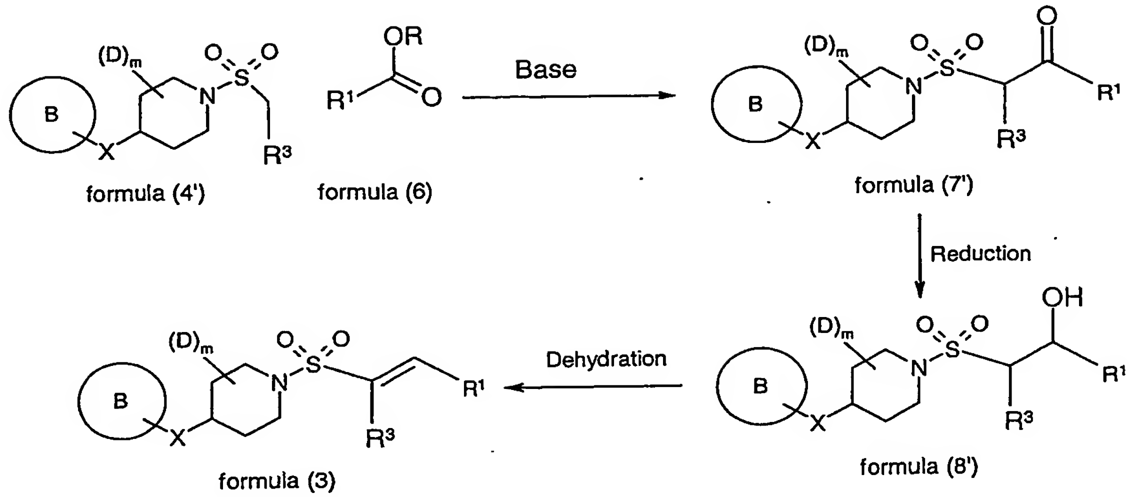
The alkene of formula (3) can be prepared by the reaction of a compound of formula (4') with a compound of formula (5) under Wadsworth-Emmons or Peterson reaction conditions;



Scheme 3

Wadsworth-Emmons or Peterson reactions involve the forming of the anion of formula (4') with 2 equivalents of lithium bis(trimethylsilyl)amide or sodium hydride or lithium diisopropylamide in THF at temperatures of –78°C to 0°C and reacting this with 1 equivalent of diethylchlorophosphate (Wadsworth Emmons) or 1 equivalent of TMSCl (Peterson). After 1h an aldehyde (1.1 equivalent) in THF is added to the resultant anion described and reacted at room temperature over 15h.

The alkene of formula (3) can also be prepared by the reaction of a compound of formula (4') with a compound of formula (6) as illustrated by scheme 4;



Scheme 4

Suitable bases include LHMDS, NaH or LDA in THF at temperatures of –78°C to 0°C to form the anion.

Suitable reducing agents for the reduction step include sodium borohydride in ethanol or borane-dimethylsulphide complex or borane-THF complex in THF at room temperature.

Suitable dehydration reagents or the dehydration step include methanesulphonylchloride or tosylchloride and triethylamine in dichloromethane at room temperature.

Or a process for the preparation of a hydroxylamine of formula (2):

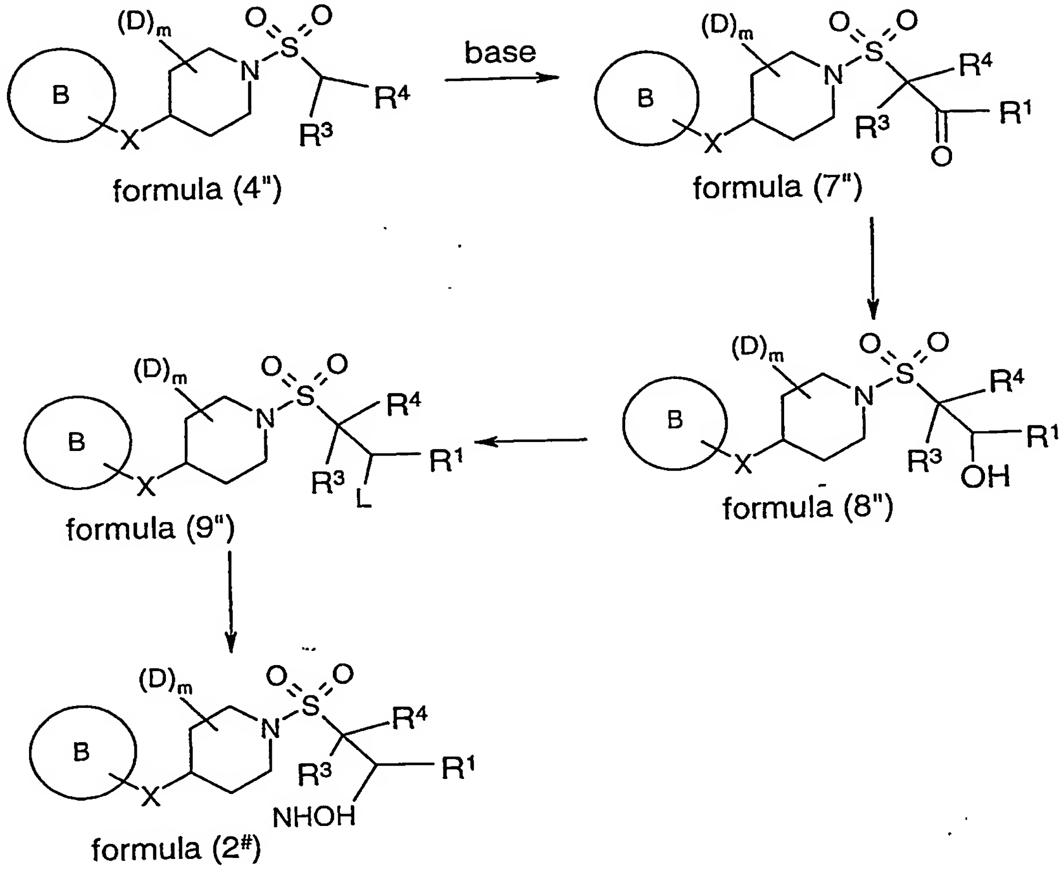
- when n is 0 (indicated as a compound of formula ($2^{\#}$)) may comprise;

c) i) reacting a compound of formula (4") (see scheme 10 for its preparation) with R^1COOR, R^1COCl or activated R^1COOR to yield a ketone of formula (7") (where R is C_{1-20}alkyl e.g. methyl, ethyl or arylC_{1-4}alkyl e.g. benzyl);

ii) reducing the ketone of formula (7") to yield an alcohol of formula (8");

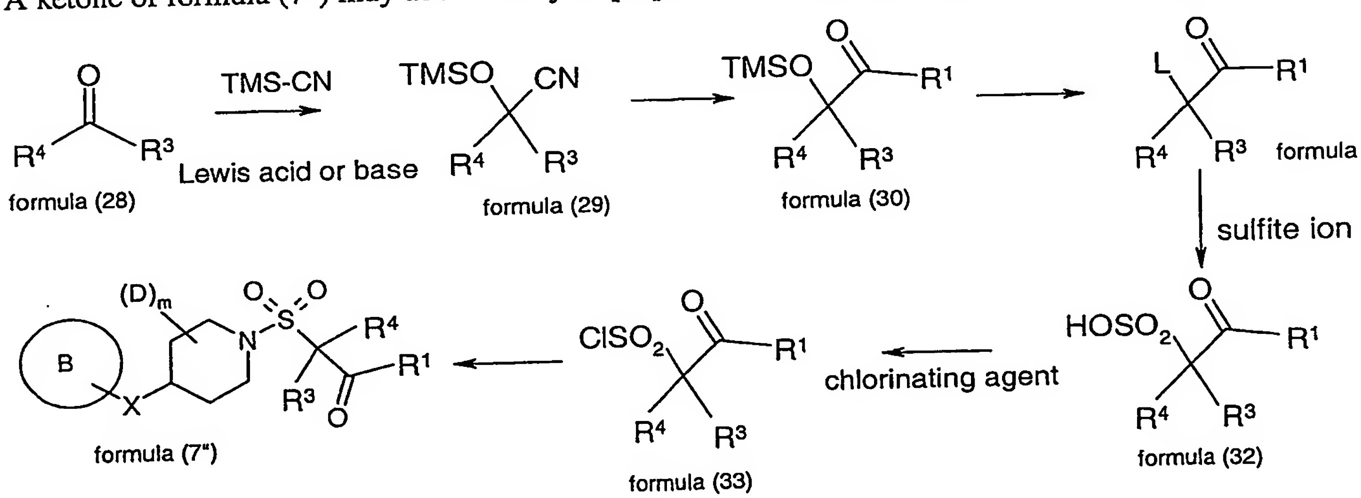
iii) converting –OH group of the alcohol of formula (8") into a leaving group (L) such as a halide, mesylate, tosylate etc. (see compound of formula (9");

iv) displacing the leaving group with aqueous hydroxylamine to yield a hydroxylamine of formula ($2^{\#}$);



Scheme 5

A ketone of formula (7") may additionally be prepared by the process illustrated in scheme 6:



Scheme 6

The silyl group present in the compound of formula (30) can be removed by TBAF.

Suitable leaving groups (L) are halo, mesyl and tosyl.

A suitable chlorinating agent is $POCl_3$.

A compound of formula (7") is prepared in the last stage by reacting the compound of formula (33) with the appropriate piperidine reagent.

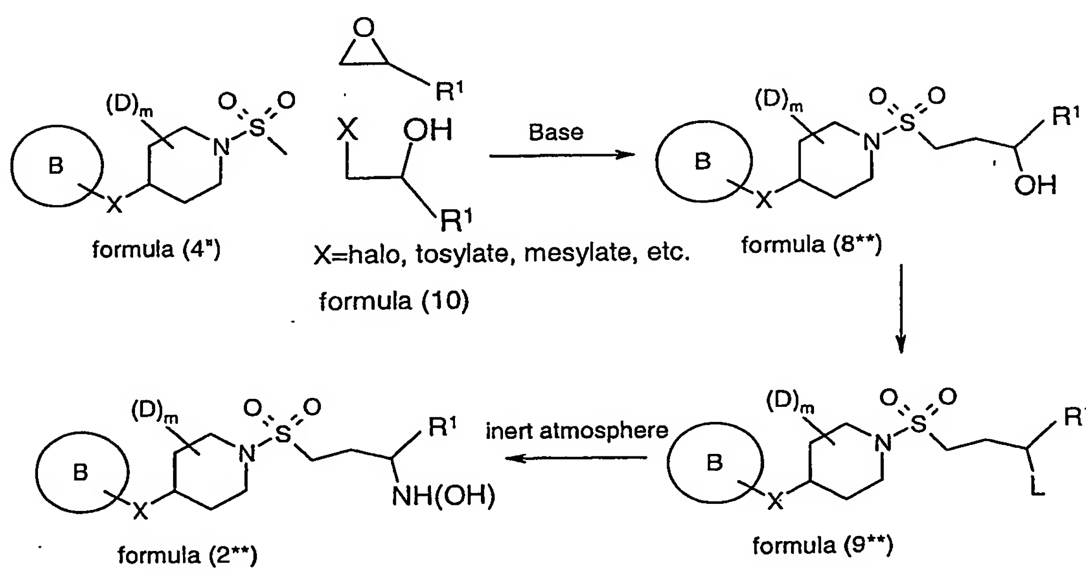
Or a process for the preparation of a hydroxylamine of formula (2):

- when n is 1 and R^3 and R^4 are both hydrogen (indicated as a compound of formula (2**)) may further comprise:

c) i) reacting a compound of formula (4") with a compound of formula (10) (either an epoxide or equivalent) to yield an alcohol of formula (8**);

ii) converting –OH group of the alcohol of formula (8**) into a leaving group such as a halide, mesylate, tosylate etc. (see compound of formula (9**);

iii) displacing the leaving group with aqueous hydroxylamine to yield a hydroxylamine of formula (2**);



Scheme 7

Suitable bases are LHMDS and lithium diisopropylamide at temperatures from –78°C to 0°C. Suitable leaving groups (L) are chloro, bromo, iodo, methanesulphonyl and tosyl and these would be formed from the alcohol by treatment with methanesulphonyl chloride and pyridine in DCM (mesylate), tosyl chloride and pyridine in DCM (tosylate), triphenylphosphine and carbon tetrabromide (bromo); the chloro, bromo and iodo derivatives could also be prepared

from the mesylate or tosylate by addition of a suitable halide source, e.g. tetrabutylammonium iodide or sodium iodide or lithium chloride in a solvent such as acetone.

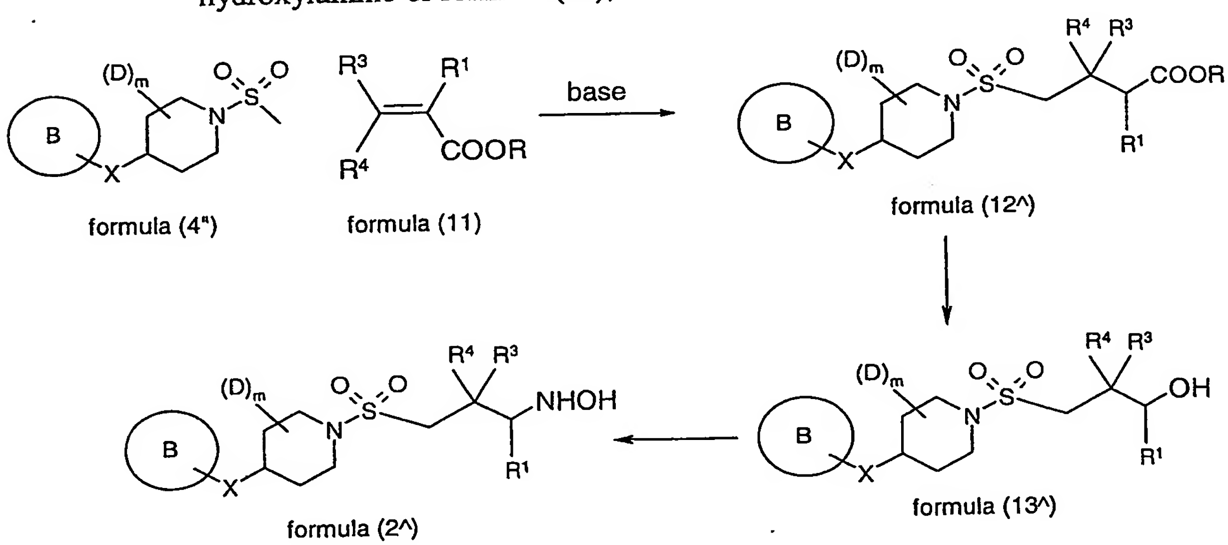
Or a process for the preparation of a hydroxylamine of formula (2):

- when n is 1, indicated as a compound of formula (2^), may further comprise:

d) i) reacting a compound of formula (4") with a compound of formula (11) to yield an ester of formula (12^);

ii) converting the ester of formula (12^) into an alcohol of formula (13^);

iii) displacing the –OH group with aqueous hydroxylamine to yield a hydroxylamine of formula (2^);



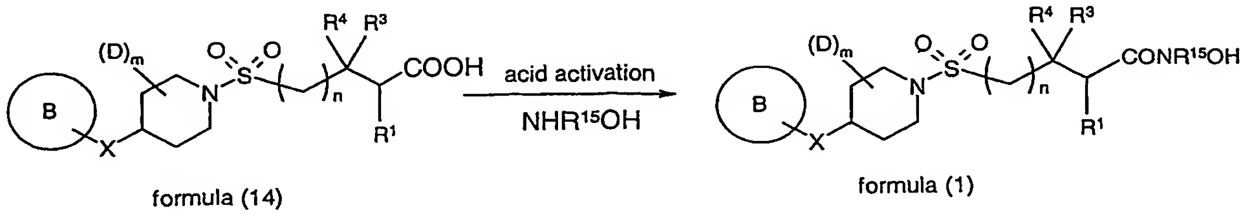
Scheme 8

The group –COOR of formula (12^) is representative of an ester wherein R may be C_{1-20} alkyl, e.g. methyl, ethyl or arylC_{1-4}alkyl, e.g. benzyl.

Baeyer-Villiger reaction conditions such as a peracid e.g. *m*-CPBA in DCM are suitable for the conversion of the ester group into the alcohol group. It may be appropriate to convert the alcohol group into a leaving group such as bromo, iodo, mesyl and tosyl, before displacement with aqueous hydroxylamine.

In another aspect the present invention provides a process for the preparation of a compound of formula **(1)** or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is $-CONR^{15}OH$, which process comprises:

a) converting an acid of formula (14) into a compound of formula (1);



Scheme 9

and thereafter if necessary:

i) converting a compound of the formula (**1**) into another compound of the formula (**1**);

ii) removing any protecting groups;

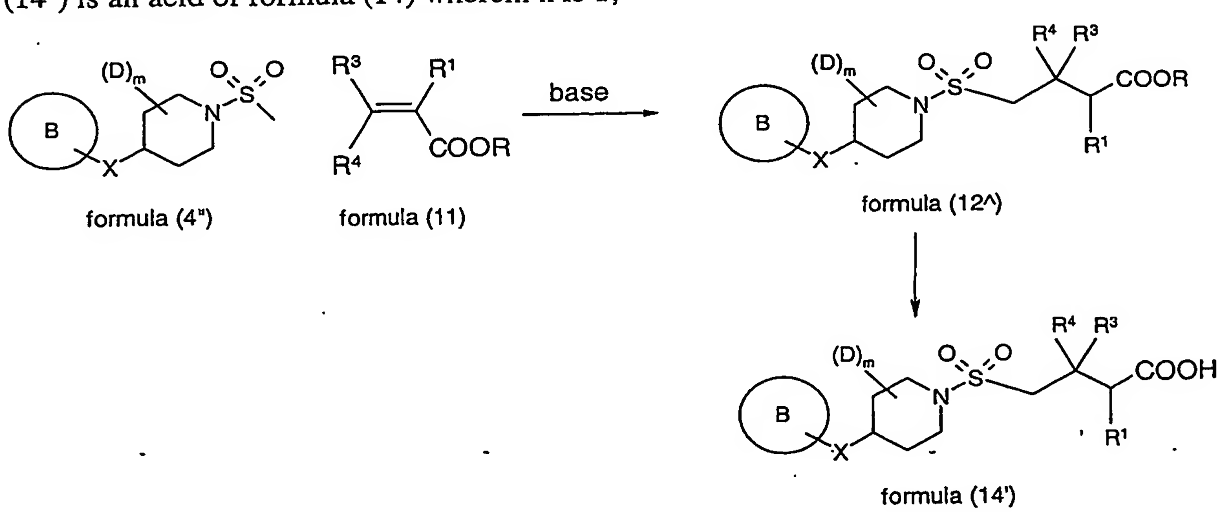
iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

The acid of formula (14) may be suitably activated by conversion to an acid halide, such as the acid chloride or to an activated ester using carbonyldiimidazole, a carbodiimide or a pentafluorophenyl ester.

Alternatively when the acid of formula (14) is an ester e.g. the methyl or ethyl ester, it can be converted directly to a compound of formula (1) by reaction with $NHR^{15}OH$.

Also provided is a process for the preparation of an acid of formula (14) which process comprises;

b) reacting a compound of formula (4") with an alkene of formula (11) to yield an ester of formula (12^) which is hydrolysed to an acid of formula (14') where an acid of formula (14') is an acid of formula (14) wherein n is 1;

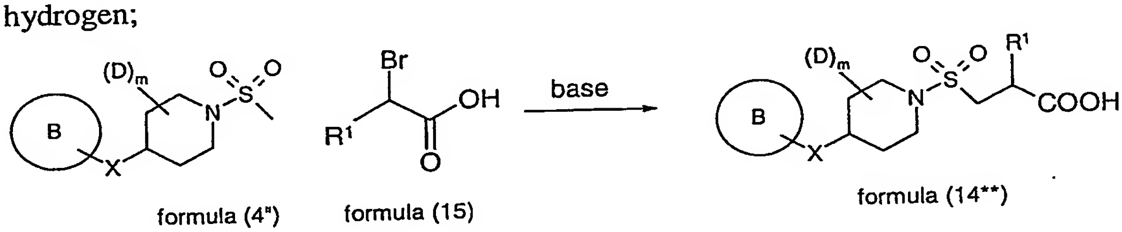


Scheme 10

Suitable bases able to deprotonate a compound of formula (4") are BuLi, LDA, LHMDS followed by the addition of a copper salt e.g. CuBr-dimethylsulphide complex, CuI, in solvents such as dimethylsulphide, ether, THF at temperatures from –78°C to RT.

Or a process for the preparation of an acid of formula (14) comprises;

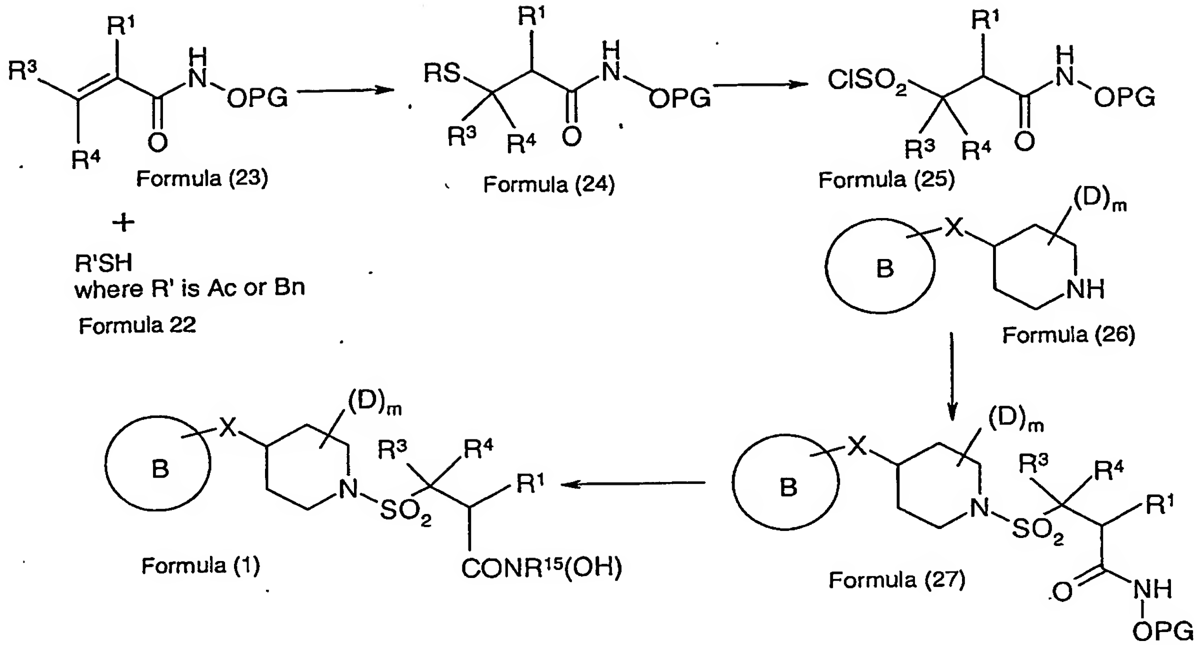
c) reacting a compound of formula (4") with a compound of formula (15) to yield an acid of formula (14**) which is an acid of formula (14) wherein n is 0, R^3 is hydrogen and R^4 is hydrogen;



Scheme 11

Suitable bases to deprotonate formula (4") include LHMDS, LDA, NaH in solvents such as THF, Ether at temperatures from –78°C to 0°C.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is $-CONR^{15}OH$ and n is 0, which process comprises steps as outlined in scheme 12:



Scheme 12

The process of scheme 12 comprises the steps of:

a) reacting a thiol of formula (22) with an acrylate of formula (23) at temperatures of 0°C to 70°C to yield a thioether of formula (24);

b) oxidising the thioether of formula (24) to a sulfonyl chloride of formula (25) by bubbling chlorine gas onto a solution of the thioether in acetic acid at temperatures of 0°C to room temperature;

c) reacting the sulfonyl choride of formula (25) with a piperidine of formula (26) under standard sulfonamide conditions (e.g. triethylamine in DCM at temperatures from 0°C to 50°C) to yield a compound of formula (27);

d) removing the protecting group to yield a compound of formula (1).

The protecting group (PG) may be benzyl- or 2,4-dimethoxybenzyl-. The former can be removed by treatment with hydrogen/ palladium and the latter by treatment with mild acid (see Tetrahedron Letters, 1998m 39(43), 7865).

The process of scheme 12 may further comprise if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any other protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

In another aspect of the invention, there is provided a process for the preparation of a compounds of formula (4), formula (4') and formula (4") which process comprises;

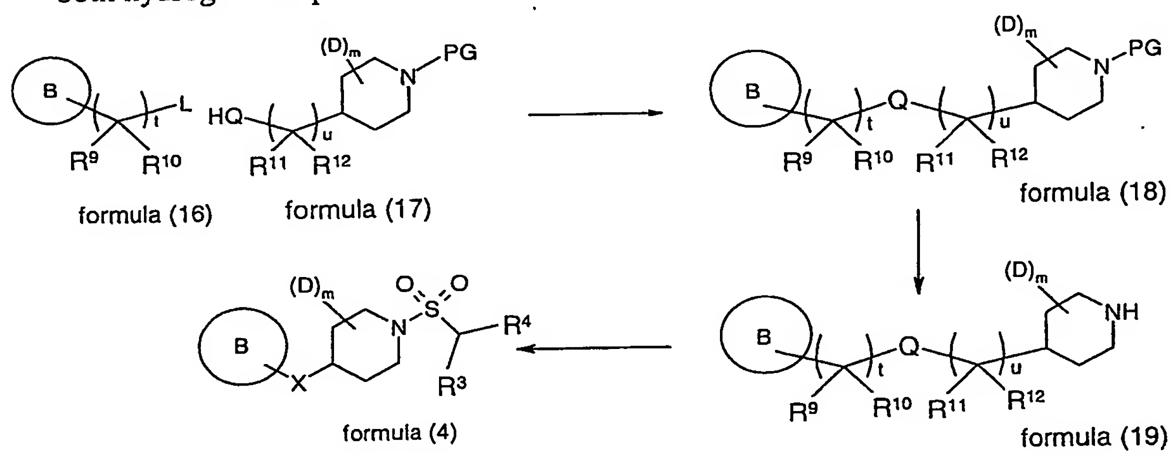
a) reacting a compound of formula (16) with a compound of formula (17) (wherein Q is not oxidised), in the presence of a base to deprotonate the compound of formula (17), to yield a compound of formula (18);

b) removing the protecting group (PG) from the compound of formula (18) to yield a compound of formula (19);.

c) reacting the compound of formula (19) with a suitable reagent to yield a compound of formula (4) wherein X is $-(CR^9R^{10})_t-Q-(CR^{11}R^{12})_u$; and

d) oxidising Q as required.

When R^4 is hydrogen a compound of formula (4') is produced and when R^3 and R^4 are both hydrogen compound of formula (4") is produced;



Scheme 13

Compounds of formula (4), formula (4') and formula (4") may also be prepared by a process which comprises;

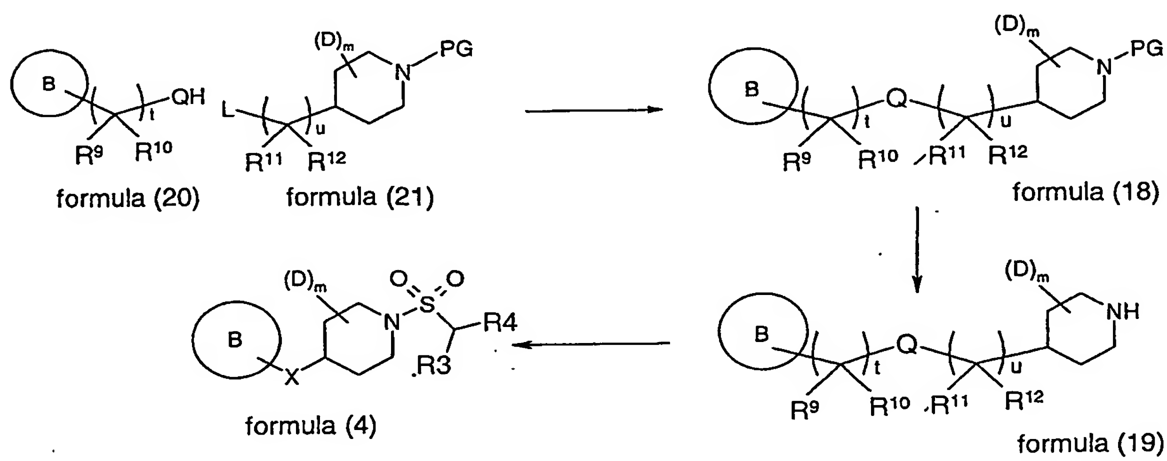
e) reacting a compound of formula (20) (wherein Q is not oxidised) with a compound of formula (21), in the presences of a base to yield a compound of formula (18);

f) removing the protecting group (PG) from the compound of formula (18) to yield a compound of formula (19);.

g) reacting the compound of formula (19) with a suitable reagent to yield a compound of formula (4) wherein X is $-(CR^9R^{10})_t-Q-(CR^{11}R^{12})_u$; and

h) oxidising Q as required.

When R^4 is hydrogen a compound of formula (4') is produced and when R^3 and R^4 are both hydrogen compound of formula (4") is produced;



Scheme 14

In both schemes 13 and 14:

L is a suitable leaving group such as halo (chloro, bromo, iodo), hydroxy, mesyl and tosyl.

Suitable bases to deprotonate a compounds of formula (17) and formula (20) include NaH, LDA, BuLi and LHMDS. Suitable reaction conditions for a) are temperatures ranging from –78°C to 70°C and an aprotic solvent, e.g. THF under argon.

Suitable protecting groups (PG) include Boc (t-butoxycarbonyl), CBz (carbonyloxybenzyl) groups and mesyl or another alkylsulphonyl-. In the case where PG is alkylsulphonyl-, reaction of formula (16) and (17) and of formula (20) and formula (21) directly produces a compound of formula (4).

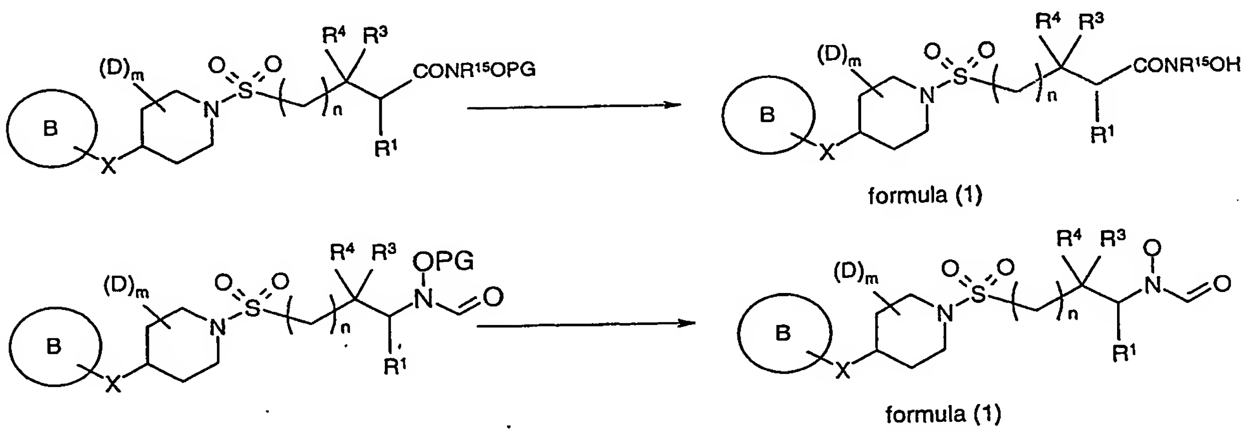
A compound of formula (18) can be converted to formula (19) by treatment with acid (Boc) or hydrogen/ palladium (CBz).

A compound of formula (19) can be converted to a compound of formula (4) by treatment with an alkylsuphonylchloride in the presence of a base such as pyridine in a solvent such as DCM.

In the case where t=0, Q is O, L is OH and B is aromatic, Mitsunobu conditions can be used to form a compound of formula (18), i.e. a compound of formula (16) or formula (20) would be reacted with a mixture of DEAD or DIAD and triphenylphosphine and a compound of formula (17) or formula (21) to give a compound of formula (4). In addition PG could also be a protected hydroxamic acid or reverse hydroxamate. Thus reaction of formula (16) and

(17) and of formula (20) and (21) would deliver a protected version of formula (1) which could then be deprotected.

A compound of formula (1) can be prepared by removal of a protecting group on the zinc binding group directly. The protecting group (PG) can be benzyl- or 2,4-dimethoxybenzyl-. The former can be removed by treatment with hydrogen/ palladium and the latter by treatment with mild acid (see Tetrahedron Letters, 1998, 39(43), 7865). The required protected hydroxamic acid or reverse hydroxamate can be obtained by using a suitably protected hydroxylamine earlier in the synthesis.



Scheme 15

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts

conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses metalloproteinases inhibitory activity, and in particular TACE inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP13.

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl2, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$\text{Fluorescence}_{\text{plus inhibitor}}$ - $\text{Fluorescence}_{\text{background}}$] divided by the [$\text{Fluorescence}_{\text{minus inhibitor}}$ - $\text{Fluorescence}_{\text{background}}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNFα convertase enzyme (TACE) may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 4 hours. The amount of inhibition is determined as for MMP13 except λex 485nm and λem 538nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*,

(1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. 160μl of heparinized (10Units/ml) human blood obtained from volunteers, was added to the plate and incubated with 20μl of test compound (duplicates), in RPMI1640 + bicarbonate, penicillin, streptomycin, glutamine and 1% DMSO, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E. coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of neat blood incubated with medium alone or LPS (6 wells/plate of each). The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

In vivo assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *in vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of female Wistar Alderley Park (AP) rats (90-100g) are dosed with compound (5 rats) or drug vehicle (5 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.) 1 hour prior to lipopolysaccharide (LPS) challenge (30μg/rat i.v.). Sixty minutes following LPS challenge rats are anaesthetised and a terminal blood sample taken via the posterior vena cavae. Blood is allowed to clot at room temperature for 2hours and serum samples obtained. These are stored at –20°C for TNFα ELISA and compound concentration analysis.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha\text{ (Vehicle control)} - \text{Mean TNF}\alpha\text{ (Treated)} \times 100}{\text{Mean TNF}\alpha\text{ (Vehicle control)}}$$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Pharmaceutical Compositions

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a

tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore in a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

Also provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNFα.

Further provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use in a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

Also provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNFα.

Further provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use as a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNFα in a warm-blooded animal such as man.

Also provided is the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided in the manufacture of a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to a further feature of this aspect of the invention there is provided a method of producing a metalloprotienase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to a further feature of this aspect of the invention there is provided a method of producing a TACE inhibitory effect in a warm-blooded animal, such as man, in

need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

Also provided is a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc,

obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Clamorgan, UK. Where Flashmaster II is referred to, this means a UV driven automated chromatography unit supplied by Jones;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

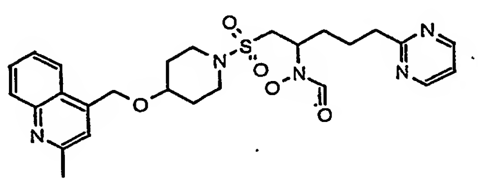
(xi) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;

NMP	*N*-methylpyrrolidinone;
DIAD	Di-*iso*propylazodicarboxylate
LHMDS or LiHMDS	Lithium bis(trimethylsilyl)amide
MeOH	Methanol
RT	Room temperature
TFA	Trifluoroacetic acid
EtOH	ethanol
EtOAc	ethyl acetate.
THF	tetrahydrofuran

EXAMPLE 1

(R/S)-1-[({4-[(2-Methylquinolinyl-4-yl)methyloxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide



To a stirred solution of (R/S)-{1-[({4-[(2-methylquinolinyl-4-yl)methyloxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl}hydroxylamine (150mg, 0.27mmol) in THF (4ml), was added a preformed mixture of acetic anhydride (200µl, 2.1mmol) and formic acid (0.8ml). The mixture was stirred at RT overnight. The solvents were removed by rotary evaporation, and the residue partitioned between EtOAc (50ml) and sodium hydrogen carbonate (20ml). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography (10g silica bond elute, eluent 0→12% EtOH / dichloromethane) to give (R/S)-1-[({4-[(2-methylquinolinyl-4-yl)methyloxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide as a white foam (76mg, 0.14mmol).

NMR: 1.7 (m, 6H), 1.9 (m, 2H), 2.6 (s, 3H), 2.85 (m, 2H), 3.1 (m, 3H), 3.4 (m, 4H), 3.7 (m, 1H), 5.0 (s, 2H), 7.3 (m, 1H), 7.45 (s, 1H), 7.5 (t, 1H), 7.7 (t, 1H), 8.1 (m, 3H), 8.7 (m, 2H), 9.7 (m, 1H); MS: 528.

The starting material (R/S)-{1-[({4-[(2-methylquinolinyl-4-yl)methyloxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl}hydroxylamine was prepared as follows :

i) To a stirred suspension of 2-methylquinoline-4-carboxylic acid (4g, 21.4mmol) in THF (100ml) at RT was added lithium aluminium hydride (21.4ml, 1.0M solution in THF, 21.4mmol) dropwise over 20mins. After 16h water (4ml) was added cautiously followed by 2N NaOH (4ml) and water (12ml). The resulting gelatinous precipitate was filtered off and washed with THF. DCM (200ml) was added to the filtrate and partitioned with saturated $NaHCO_3$ (2x75ml). The organic layer was dried ($MgSO_4$), concentrated, triturated with DCM & filtered to give 2-methylquinoline-4-methylalcohol as a white powder (858mg, 5mmol). The mother liquours were purified by chromatography (20g silica bond elute, eluent 0→5% EtOH / DCM) to give a further 610mgs of product (3.5mmol).
NMR: 2.6 (s, 3H), 5.0 (d, 2H), 5.5 (t, 1H), 7.4 (s, 1H), 7.5 (t, 1H), 7.7 (t, 1H) and 7.9 (m, 2H); MS: 174.

ii) To a suspension of 2-methylquinoline-4-methylalcohol (100mg, 0.58mmol) in DCM (5ml) at RT was added triethylamine (0.24ml, 1.74mmol). The reaction mixture was then cooled to 0°C and methanesulphonylchloride (0.05ml, 0.64mmol) was added dropwise. After 10mins the reaction mixture was concentrated and EtOAc (20ml) was added and the organic layer partitioned with brine (10ml), dried ($MgSO_4$), concentrated and purified by chromatography (10g silica bond elute, eluent 5% MeOH / DCM) to give 2-methylquinoline-4-methyloxysulphonylmethane (110mg, 0.44mmol).
NMR: 2.7 (s, 3H), 3.35 (s, 3H), 5.75 (s, 2H), 7.5 (s, 1H), 7.6 (t, 1H), 7.75 (t, 1H), 8.0 (m, 2H): MS: 252.

iii) To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (1.75g, 8.73mmol) in DMF (20ml) at 0°C was added sodium hydride (419mg, 60% dispersion in oil, 10.5mmol). After 10mins a solution of 2-methylquinoline-4-methyloxysulphonylmethane (2.19g, 8.73mmol) in DMF (10ml) was added dropwise over 5mins at 0°C. After 5h the mixture was concentrated and the residue taken up in EtOAc (150ml). The organic layer was washed with brine (50ml), dried ($Na_2S_2O_4$), concentrated and purified by chromatography (MPLC, eluting with 75% EtOAc/ hexane) to give *tert*-butyl 4-(2-methylquinoline-4-methyloxy)piperidine-1-carboxylate (1.46g, 4.1mmol).
MS: 357.

iv) To a solution of *tert*-butyl 4-(2-methylquinoline-4-methyloxy)piperidine-1-carboxylate (1.45g, 4.1mmol) in DCM (10ml) at RT was added TFA (3ml). After 15h the mixture was concentrated and azeotroped with toluene (x2) to give 4-(2-methylquinoline-4-methyloxy)-piperidine.di TFA salt (1.97g, 4.1mmol).
MS: 257.

v) To a solution of 4-(2-methylquinoline-4-methyloxy)-piperidine.di TFA salt (2.49g, 5.2mmol) in DCM (40ml) at 0°C was added triethylamine (4.3ml, 31mmol) followed by dropwise addition of methanesulphonylchloride (0.8ml, 10.3mmol) dropwise over 1min and the reaction mixture was allowed to warm to RT. After 15h the mixture was diluted with DCM (60ml), washed with water (30ml), brine (25ml), concentrated and purified by chromatography (MPLC, eluting with 100% EtOAc) to give 4-(2-methylquinoline-4-methyloxy)-piperidinylsulphonylmethane (600mg, 1.8mmol) as a pale yellow solid.
NMR: 1.6 (m, 2H), 2.0 (m, 2H), 2.65 (s, 3H), 2.85 (s, 3H), 3.0 (m, 2H), 3.3 (m, 2H), 3.7 (m, 1H), 5.0 (s, 2H), 7.4 (s, 1H), 7.5 (t, 1H), 7.7 (t, 1H), 7.9 (d, 1H) and 8.0 (d, 1H); MS: 335.

vi) To a stirred solution of 4-(2-methylquinoline-4-methyloxy)-piperidinylsulphonylmethane (150mg, 0.45mmol) in THF (6ml) at -10°C under argon was added LHMDS (0.945ml, 1M in THF, 0.945mmol) and after a further 15 mins, diethyl chlorophosphate (0.065ml, 0.45mmol) was added. After 1h a solution of 4-(2-pyrimidinyl)-butanal§ (75mg, 0.495mmol) in THF (0.2ml) was added and the mixture allowed to warm to RT over the weekend. Saturated ammonium chloride (8ml) was then added and the organic layer separated. The aqueous layer was re-extracted with EtOAc (8ml) and the combined organics were concentrated and purified by chromatography (10g silica bond elute, eluent 0→6% EtOH / DCM) to give *E*-1-{4-(2-methylquinoline-4-methyloxy)-piperidin-1-ylsulphonyl}-5-(pyrimidin –2- yl)pent-1-ene as a pale yellow oil (0.13g, 0.28mmol). NMR: 1.2 (m, 1H), 1.7 (m, 2H), 1.9 (m, 4H), 2.3 (m, 1H), 2.65 (s, 3H), 2.9 (m, 4H), 3.3 (m, 1H), 3.65 (m, 1H), 4.0 (m, 1H), 5.0 (s, 2H), 6.5 (m, 2H), 7.3 (m, 1H), 7.4 (d, 1H), 7.5 (m, 1H), 7.7 (m, 1H), 7.9 (m, 1H), 8.0 (m, 1H) and 8.7 (m, 2H); MS: 467.

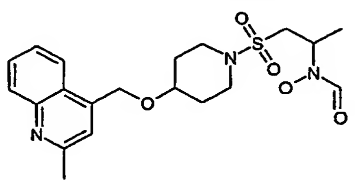
vii) To a stirred solution of the *E*-1-{4-(2-methylquinoline-4-methyloxy)-piperidin-1-ylsulphonyl}-5-(pyrimidin –2- yl)pent-1-ene (125mg, 0.27mmol) in THF (7ml) under argon

was added hydroxylamine (50% solution in water, 3ml) and the mixture stirred overnight. The mixture was poured into water (10ml) and EtOAc (50ml) and the partitioned organic layer was dried ($MgSO_4$) and concentrated to give (R/S)-{1-[({4-[(2-methylquinolinyl-4-yl)methyloxy]piperidin-1-yl}sulfonyl)methyl]-4-pyrimidin-2-ylbutyl}hydroxylamine (150mg, 0.27mmol); MS: 500.

§ 4-(2-pyrimidinyl)-butanal has been reported in the literature and has CAS registry number 260441-10-9 (CA Index Name: 2-pyrimidinebutanal).

EXAMPLE 2

(R/S)-1-methyl-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide

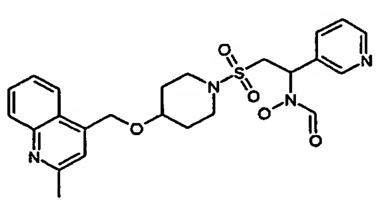


The procedure described in Example 1 was followed except that 4-(2-methylquinoline-4-methyloxy)-piperidinylsulphonylmethane (150mg, 0.45mmol) (synthesis described above) was reacted with acetaldehyde (0.028ml, 0.495mml) instead of 4-(2-pyrimidinyl)-butanal to give 1-methyl-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide (47mg, 0.11mmol).

NMR: 1.2 (m, 3H), 1.7 (m, 2H), 2.0 (m, 2H), 2.65 (s, 3H), 3.05 (m, 3H), 3.4 (m, 4H), 3.7 (m, 1H), 5.0 (s, 2H), 7.4 (s, 1H), 7.5 (t, 1H), 7.7 (t, 1H) and 8.0 (m, 3H); MS: 422.

EXAMPLE 3

(R/S)-1-pyrid-3-yl-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide



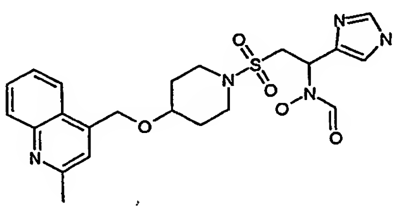
The procedure described in Example 1 was followed except that 4-(2-methylquinoline-4-methyloxy)-piperidinylsulphonylmethane (150mg, 0.45mmol) (synthesis described above)

was reacted with pyridine-3-carboxaldehyde (0.047ml, 0.495mml) instead of 4-(2-pyrimidinyl)-butanal to give (R/S)-1-pyrid-3-yl-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide (74mg, 0.15mmol).

NMR: 1.6 (m, 2H), 1.9 (m, 2H), 2.6 (m, 3H), 3.0 (m, 2H), 3.0 (m, 4H), 3.75 (m, 2H), 5.0 (s, 2H), 7.4 (m, 2H), 7.5 (t, 1H), 7.7 (t, 1H), 7.9 (m, 2H), 8.0 (d, 1H), 8.2 (s, 1H), 8.5 (m, 1H) and 8.6 (m, 1H); MS: 485.

<u>EXAMPLE 4</u>

(R/S)-1-(1*H*-imidazol-4-yl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide

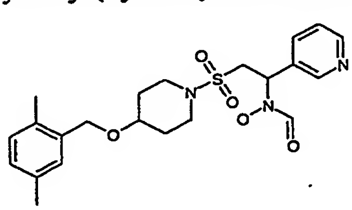


The procedure described in Example 1 was followed except that 4-(2-methylquinoline-4-methyloxy)-piperidinylsulphonylmethane (150mg, 0.45mmol) (synthesis described above) was reacted with imidazole-5-carboxaldehyde (48mg, 0.495mml) instead of 4-(2-pyrimidinyl)-butanal to give (R/S)-1-(1*H*-imidazol-4-yl)-2-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)ethyl(hydroxy)formamide, which was purified using a 10g SCX column (eluting with 100% MeOH followed by 10% aqueous ammonia, MeOH) (39mg, 0.15mmol).

NMR: 1.6 (m, 2H), 2.0 (m, 2H), 2.65 (s, 3H), 3.0 (m, 2H), 3.2 (m, 2H), 3.3 (m, 2H), 3.7 (m, 2H), 5.0 (s, 2H), 7.1 (s, 1H), 7.5 (m, 3H), 7.7 (m, 2H), and 8.0 (m, 3H); MS: 474.

<u>EXAMPLE 5</u>

(R/S)-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide



To a stirred solution of (R/S)-1-[({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl]- 3-pyridylmethyl hydroxylamine (130mg, 0.31mmol) in THF (2.5ml), was added a preformed mixture of acetic anhydride (100µl) and formic acid (0.4ml). The mixture was stirred at RT overnight. The solvents were removed by rotary evaporation, and saturated sodium hydrogen carbonate (4ml) was added. EtOAc (10ml) was added and the mixture separated. The aqueous layer was reextracted with EtOAc (5ml) and the combined organic layer was concentrated in the presence of MeOH (10ml) and purified by chromatography (10g silica bond elute, eluent 0→100% EtOH / DCM followed by 5% EtOH/ EtOAc) to give (R/S)-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-pyridin-3-ylethyl(hydroxy)formamide as a foam (64mg, 0.14mmol). MS: 447.

The starting material (R/S)-1-[({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl]-3-pyridylmethyl hydroxylamine was prepared as follows :

i) To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (4g, 19.9mmol) in DMF (100ml) at RT was added sodium hydride (796mg, 60% dispersion in oil, 19.9mmol). After 1h 2,5-dimethylbenzyl chloride (2.94ml, 19.9mmol) was added dropwise. After 16h water was added (5ml) and the DMF removed *in vacuo*. The mixture was partitioned between water (100ml) and DCM (3x200ml) and the combined organic layer was, dried ($MgSO_4$), concentrated and purified by chromatography (MPLC, eluting with 0→20% EtOAc/ DCM) to give *tert*-butyl 4-(2,5-dimethylbenzyloxy)piperidine-1-carboxylate as a green oil (4.15g, 13mmol).

NMR: 1.4 (m, 11H), 1.8 (m, 2H), 2.2 (d, 6H), 3.0 (m, 2H), 3.6 (m, 3H), 4.4 (s, 2H), 7.0 (m, 2H), 7.1 (s, 1H); MS: 320.

ii) To a solution of *tert*-butyl 4-(2,5-dimethylbenzyloxy)piperidine-1-carboxylate (4.1g, 12.85mmol) in DCM (30ml) was added TFA (3ml) and the mixture stirred overnight at RT. TFA (3ml) was added and the mixture stirred at 40°C. After 1h the mixture was concentrated and the residue azeotroped with toluene to give 4-(2,5-dimethylbenzyloxy)piperidine.TFA salt as a colourless oil (5.52g, 12.85mmol plus a small amount of toluene).

NMR: 1.7 (m, 2H), 2.0 (m, 2H), 2.2 (s, 3H), 2.25 (s, 3H), 3.0 (m, 2H), 3.2 (m, 2H), 3.65 (m, 1H), 4.45 (s, 2H), 7.0 (m, 2H) and 7.1 (s, 1H): MS: 220.

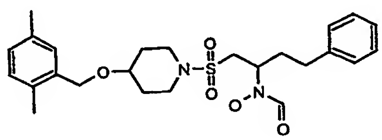
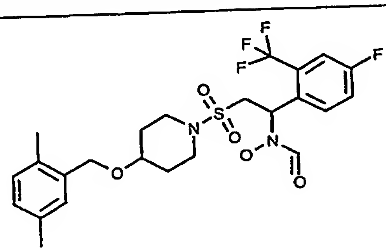
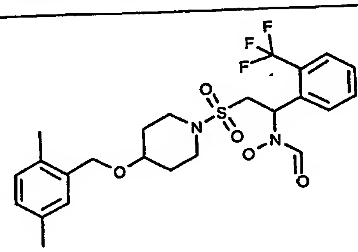
iii) To a solution of 4-(2,5-dimethylbenzyloxy)piperidine.TFA salt (5.51g, 12.85mmol plus a small amount of toluene) in DCM (90ml) at 0°C was added triethylamine (8.59ml, 61.6mmol) followed by dropwise addition of methanesulphonylchloride (1.05ml, 13.6mmol) dropwise over 5mins and the reaction mixture was allowed to warm to RT. After 63h the mixture was diluted with DCM (90ml), washed with water (50ml), brine (50ml), dried ($MgSO_4$) and concentrated to give a light brown oil. The oil was triturated with EtOH (20ml), filtered and washed with cold EtOH and concentrated to give 4-(2,5-dimethylbenzyloxy)piperidinylsulfonylmethane as a white solid (2.63g, 8.0mmol). NMR: 1.6 (m, 2H), 1.9 (m, 2H), 2.2 (s, 3H), 2.25 (s, 3H), 2.85 (s, 3H), 3.0 (m, 2H), 3.55 (m, 1H), 4.45 (s, 2H), 7.0 (m, 2H) and 7.1 (s, 1H); MS: 298.

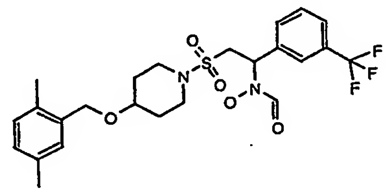
iv) To a stirred solution of 4-(2,5-dimethylbenzyloxy)piperidinylsulfonylmethane (200mg, 0.67mmol) in THF (8ml) at -10°C under argon was added LHMDS (1.48ml, 1M in THF, 1.48mmol) and after a further 15 mins, diethyl chlorophosphate (0.086ml, 0.67mmol) was added. After 1h a solution of pyridine 3-carboxaldehyde (70mg, 0.74mmol) in THF (0.5ml) was added and the mixture allowed to warm to RT over the weekend. Saturated ammonium chloride (10ml) was then added and the organic layer separated. The aqueous layer was re-extracted with EtOAc (10ml) and the combined organics were concentrated and purified by chromatography (10g silica bond elute, eluent 5→100% EtOAc / hexane) to give *E*-1-{4-(2,5-dimethylbenzyloxy)-piperidin-1-ylsulphonyl}3-pyridylethene as a clear gum (0.09g, 0.23mmol). MS: 387.

v) To a stirred solution of the *E*-1-{4-(2,5-dimethylbenzyloxy)-piperidin-1-ylsulphonyl}-3-pyridylethene (90mg, 0.23mmol) in THF (5ml) under argon was added hydroxylamine (50% solution in water, 2ml) and the mixture stirred for 4d. The mixture was poured into water (2ml) and EtOAc (10ml) and the partitioned organic layer was dried ($MgSO_4$) and concentrated to give (R/S)-1-[({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)methyl] 3-pyridylmethyl hydroxylamine (96mg, 0.23mmol); MS: 420.

EXAMPLES 6-9

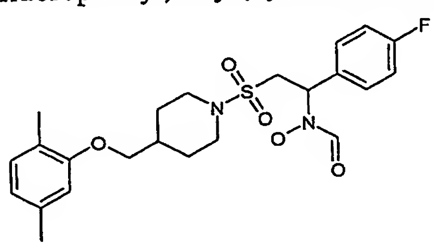
The procedures described in Example 5 were followed using 4-(2,5-dimethylbenzyloxy)piperidinylsulfonylmethane (described above) with the aldehyde highlighted in the table in place of 4-(2-pyrimidinyl)-butanal.

Example No.	Structure and Name	Aldehyde starting material	MS of final product
6	 (R/S)-[1-({[4-(2,5-Dimethylbenzyloxy)piperidin-1-yl]sulfonyl}methyl)-3-phenylpropyl]hydroxyformamide	3-Phenylpropan-1-al	475
7	 (R/S)-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-[4-fluoro-2-(trifluoromethyl)phenyl]ethyl(hydroxy)formamide	4-Fluoro-2-trifluoromethylbenzaldehyde	533
8	 (R/S)-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-[2-(trifluoromethyl)phenyl]ethyl(hydroxy)formamide	2-Trifluoromethylbenzaldehyde	515

Example No.	Structure and Name	Aldehyde starting material	MS of final product
9	 (R/S)-2-({4-[(2,5-dimethylbenzyl)oxy]piperidin-1-yl}sulfonyl)-1-[3-(trifluoromethyl)phenyl]ethyl(hydroxy)formamide	3-Trifluoromethylbenzaldehyde	515

EXAMPLE 10

(R/S)-2-({4-[(2,5-Dimethylphenoxy)methyl]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethyl(hydroxy)formamide



To a stirred solution of (R/S)-2-({4-[(2,5-dimethylphenoxy)methyl]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethylhydroxylamine (185mg, 0.42mmol) in THF (5ml), was added a preformed mixture of acetic anhydride (200µl, 2.1mmol) and formic acid (0.8ml). The mixture was stirred at RT overnight. The solvents were removed by rotary evaporation, and the residue was stirred in a mixture of EtOAc and saturated sodium hydrogen carbonate for 2h, then the layers were separated and the organic layer was washed with water, dried (Na_2SO_4), concentrated and purified by chromatography (10g silica bond elute, eluent 50→100% EtOAc/ Hexane; then on MPLC, eluent 25→75% EtOAc/ DCM; then on a 20g silica bond elute, eluent 30→100% EtOAc/ DCM) to give (R/S)-2-({4-[(2,5-dimethylphenoxy)methyl]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethyl(hydroxy)formamide as a pale-yellow foam (90mg, 0.19mmol).

NMR: 1.3 (m, 4H), 1.8 (m, 3H), 2.1 (s, 3H), 2.25 (s, 3H), 2.8 (m, 2H), 3.3 (m, 1H), 3.6 (m, 2H), 3.8 (d, 2H), 6.6 (d, 1H), 6.7 (s, 1H), 7.0 (d, 1H), 7.2 (t, 2H), 7.5 (m, 2H), 8.2 (s, 1H); MS: 465.

The starting material (R/S)-2-({4-[(2,5-dimethylphenoxy)methyl]piperidin-1-yl}sulfonyl)-1-(4-fluorophenyl)ethylhydroxylamine was prepared as follows :

i) To a stirred solution of piperidin-4-ylmethanol (2.85g, 24.8mmol) dissolved in DMF (130ml) at 0°C was added triethylamine (13.8ml, 99.2mmol) followed by methanesulphonyl chloride (4.8ml, 62mmol) dropwise over 5mins and the reaction mixture allowed to warm to RT. After 16h the reaction mixture was concentrated and then residue was partitioned between water (50ml) and DCM (3x150ml). The combined organics were dried (Na_2SO_4), concentrated and triturated with EtOH to give 4-(methanesulphonyloxymethyl)piperidinylsulphonylmethane as a pale yellow solid (3.2g, 11.8mmol).
NMR: 1.3 (m, 2H), 1.8 (m, 3H), 2.7 (m, 2H), 2.85 (s, 3H), 3.15 (s, 3H), 3.6 (m, 2H), 4.1 (d, 2H); MS: 272.

ii) To a stirred solution of 2,5-dimethylphenol (298mg, 2.4mmol) and 4-(methanesulphonyloxymethyl)piperidinylsulphonylmethane (600mg, 2.2mmol) in DMF (10ml) was added sodium hydride (132mg, 3.6mmol) and the mixture was heated to 60°C. After 1h the mixture was cooled, concentrated and triturated with EtOH to give a brown solid. This solid was treated with saturated sodium hydrogen carbonate, filtered and dried under vacuum to give 4-(2,5-dimethylphenyloxymethyl)piperidinylsulphonylmethane as a white powdery solid (518mg, 1.95mmol).
NMR: 1.4 (m, 2H), 1.9 (m, 3H), 2.1 (s, 3H), 2.25 (s, 3H), 2.7 (m, 2H), 2.85 (s, 3H), 3.6 (m, 2H), 3.8 (d, 2H), 6.6 (d, 1H), 6.7 (s, 1H) and 7.0 (1H); MS: 298.

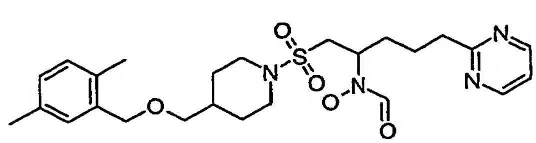
iii) To a stirred solution of 4-(2,5-dimethylphenyloxymethyl)piperidinylsulphonylmethane (200mg, 0.67mmol) in THF (8ml) at -10°C under argon was added LHMDS (1.48ml, 1M in THF, 1.48mmol) and after a further 15 mins, diethyl chlorophosphate (0.097ml, 0.67mmol) was added. After 1.5h 4-fluorobenzaldehyde (0.079ml, 0.74mmol) was added and the mixture allowed to warm to RT overnight. Saturated ammonium chloride (10ml) was then added and the organic layer

separated. The aqueous layer was re-extracted with EtOAc (10ml) and the combined organics were dried (Na_2SO_4), concentrated and purified by chromatography (10g silica bond elute, eluent 5→10% EtOAc / Hexane) to give *E*-1-{4-(2,5-dimethylphenyloxymethyl)-piperidinylsulphonyl}-2-(4-fluorophenyl)ethene as a white waxy solid (0.21g, 0.5mmol). NMR: 1.4 (m, 2H), 1.9 (m, 3H), 2.0 (s, 3H), 2.25 (s, 3H), 2.7 (m, 2H), 3.6 (d, 2H), 3.8 (d, 2H), 6.6 (d, 1H), 6.7 (s, 1H), 6.95 (d, 1H), 7.2 (m, 3H), 7.4 (m, 1H) and 7.8 (m, 2H); MS: 404.

iv) To a stirred solution of the *E*-1-{4-(2,5-dimethylphenyloxymethyl)-piperidinylsulphonyl}-2-(4-fluorophenyl)ethene (200mg, 0.5mmol) in THF (5ml) under argon was added hydroxylamine (50% solution in water, 1.5ml) and the mixture stirred over the weekend. Saturated ammonium chloride (8ml) was added and the layers separated. The aqueous layer was partitioned with DCM (10ml) and the combined organics were dried (Na_2SO_4), concentrated and purified by chromatography (10g silica bond elute, eluent 50→100% EtOAc / Hexane; then 20g silica bond elute, eluent 50→100% EtOAc / Hexane) to give R/S-*N*-[1-([4-(2,5-dimethylphenyloxymethyl)piperidino]sulfonylmethyl)-4-fluorophenylmethyl]hydroxylamine as a colourless oil (170mg, 0.39mmol); NMR: 1.3 (m, 2H), 1.8 (m, 3H), 2.1 (s, 3H), 2.25 (s, 3H), 2.8 (m, 2H), 3.6 (m, 3H), 3.8 (d, 2H), 4.2 (m, 1H), 5.9 (br s, 1H), 6.6 (d, 1H), 6.7 (s, 1H), 7.0 (d, 1H), 7.15 (m, 2H), 7.4 (m, 2H); MS: 437.

<u>**EXAMPLE 11**</u>

(R/S)-1-{[(4-{[(2,5-dimethylbenzyl)oxy]methyl}piperidin-1-yl)sulfonyl]methyl}-4-pyrimidin-2-ylbutyl(hydroxy)formamide



The procedure described in Example 1 was followed using 4-(2,5-dimethylbenzyloxymethyl)piperidinylsulphonylmethane (synthesis described below) (171mg, 0.36mmol) in place of to give (R/S)-1-{[(4-{[(2,5-dimethylbenzyl)oxy]methyl}piperidin-1-yl)sulfonyl]methyl}-4-pyrimidin-2-ylbutyl(hydroxy)formamide (57mg, 0.113mmol). MS: 505.

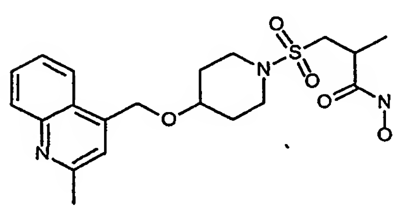
The synthesis of 4-(2,5-dimethylbenzyloxymethyl)piperidinylsulphonylmethane was achieved as shown below:

i). To a stirred solution of 2,5-dimethylbenzyl alcohol (500ul, 3.7mmol) in DMF (15ml) was added sodium hydride (180mg, 4.9mmol) at RT. After 90mins a solution of 4-(methanesulphonyloxymethyl)piperidinylsulphonylmethane (1.09g, 4.0mmol) in DMF (15ml) was added and the reaction left to stir overnight at RT. Water (5ml) was added and the solvent evaporated. The residue was then partitioned between EtOAc (40ml) and brine (25ml) and the aqueous layer re-extracted with EtOAc (25ml). The combined organic layer was dried (Na_2SO_4), concentrated and purified by chromatography (Flashmaster II) to give 4-(2,5-dimethylbenzyloxymethyl)piperidinylsulphonylmethane as a white solid (400mg, 1.3mmol).

NMR: 1.37 (m, 2H), 1.76 (m, 1H), 1.87 (m, 2H), 2.28 (s, 3H), 2.31 (s, 3H), 2.64 (m, 2H), 2.76 (s, 3H), 3.35 (d, 2H), 3.8 (m, 2H), 4.45 (s, 2H), 7.0-7.09 (m, 3H).

EXAMPLE 12

(R/S)-2-Methyl-3-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)propionic hydroxamic acid



To a stirred solution of (R/S)-2-methyl-3-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)propionic acid (110mg, 0.27mmol) (described below) in DCM (4ml) at 0°C was added DMF (0.05ml) and oxalyl chloride (0.03ml, 0.32mmol) dropwise. After 45mins at 0°C the reaction mixture was concentrated *in vacuo* and dried under vacuum for 1h to give the acid chloride as a light brown foam. To a stirred solution of hydroxylamine (50% aqueous solution, 0.3ml) in THF (5ml) at RT was added a solution of the acid chloride in DCM (2ml) dropwise over 5 mins. After 1h the reaction mixture was diluted with EtOAc (20ml) and treated with saturated ammonium chloride (10ml). The organic layer was dried (Na2SO4), concentrated, triturated with ether, filtered and dried *in vacuo* to give (R/S)-2-methyl-3-({4-

[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)propionic hydroxamic acid as an off-white solid (77mg, 0.18mmol). Melting Point: 184.7oC; NMR: 1.1 (d, 3H), 1.7 (m, 2H), 1.95 (m, 2H), 2.65 (s, 3H), 3.0 (m, 3H), 3.4 (m, 4H), 3.7 (m, 1H), 5.0 (s, 2H), 7.45 (s, 1H), 7.5 (t, 1H), 7.7 (t, 1H), 7.9 (d, 1H), 8.05 (d, 1H), 8.8 (s, 1H) and 10.55 (br s, 1H); MS: 422.5.

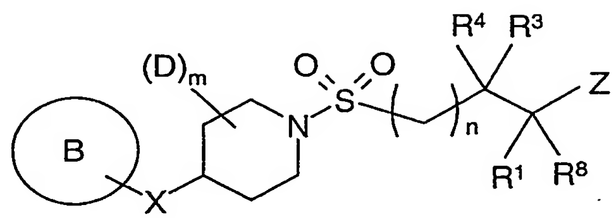
The (R/S)-2-methyl-3-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)propionic acid described above was prepared as follows:

i) To a stirred suspension of 4-(2-methylquinoline-4-methyloxy)-piperidinylsulphonylmethane (400mg, 1.2mmol) (synthesis described above) in THF (4ml) at -10°C under argon was added LHMDS (1.26ml, 1M in THF, 1.26mmol). Immediately after this to a separate stirred solution of 2-bromopropionic acid (0.12ml, 1.26mmol) in THF (4ml) at -10°C under argon was added LHMDS (1.32ml, 1M in THF, 1.32mmol). After 10mins this solution was added to the first solution over 5mins. After 1h saturated ammonium chloride (10ml) was added, the reaction mixture acidified with glaciel acetic acid and extracted with EtOAc (2x30ml). The combined organic extracts were dried (Na2SO4), concentrated and azeotroped with toluene to give a brown gum. This was then purified by chromatography (10g silica bond elute, eluent 0→10% EtOH in DCM) to give (R/S)-2-methyl-3-({4-[(2-methylquinolin-4-yl)methoxy]piperidin-1-yl}sulfonyl)propionic acid as a yellow foam (280mg, 0.69mmol). NMR: 1.25 (d, 3H), 1.7 (m, 2H), 2.0 (m, 2H), 2.65 (s, 3H), 2.8 (m, 1H), 3.05 (m, 3H), 3.4 (m, 3H), 3.7 (m, 1H), 5.0 (s, 2H), 7.4 (s, 1H), 7.5 (t, 1H), 7.7 (t, 1H), 7.9 (d, 1H), 8.05 (d, 1H); MS: 407.

CLAIMS:

What we claim is :-

1. A compound of formula (1):



formula (1)

wherein Z is selected from $-CONR^{15}OH$ and $-N(OH)CHO$;

R^{15} is hydrogen or C_{1-3}alkyl;

wherein R^1 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, C_{1-4}alkoxycarbonyl, $-OR^5$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-COR^2$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^{16}COR^5$, $-SO_2NR^5R^6$ and $-NR^{16}SO_2R^2$;

R^{16} is hydrogen or C_{1-3}alkyl;

R^{17} is selected from halo, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy;

R^2 is group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^5 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^6 is hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^5 and R^6 together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

wherein R^8 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy and C_{1-4}alkyl;

or R^1 and R^8 together form a carbocyclic or saturated heterocyclic 3- to 6-membered ring;

wherein R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-7}cycloalkenyl, heterocyclyl, aryl or heteroaryl;

wherein n is 0 or 1;

wherein m is 0 or 1;

wherein D is hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl or fluoro;

wherein X is $-(CR^9R^{10})_t-Q-(CR^{11}R^{12})_u-$ where t and u are independently 0 or 1 with the proviso that t and u cannot both be 0;

wherein Q is O, S, SO or SO_2;

R^9, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

wherein B is a group selected from aryl, heteroaryl, heterocyclyl, C_{3-10}cycloalkyl, C_{5-7}cycloalkenyl, where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethyloxy, halo, C_{1-4}alkyl (optionally substituted by one or more R^{13}), C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{13}), heterocycloalkyl, heteroaryl, $-OR^{13}$, cyano, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{16}COR^{13}$, $-SO_2NR^{13}R^{14}$, $-NR^{16}SO_2R^{13}$, $-SR^{13}$, $-SOR^7$ and $-SO_2R^7$;

R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl

R^{13} and R^{14} are independently hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^{13} and R^{14} together with the nitrogen to which they are attached form a carbocyclic or heterocyclic 5 to 7-membered ring;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, for use as a medicament.

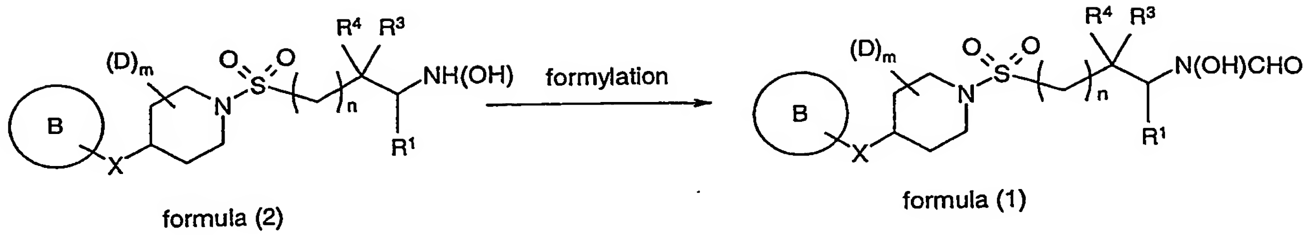
3. The use of a compound according to Claim 1 in the manufacture of a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes.

4. The use of a compound according to Claim 1 in the manufacture of a medicament in the treatment of a disease condition mediated TNFα.

5. A pharmaceutical composition comprising a compound according to Claim 1; and a pharmaceutically-acceptable diluent or carrier.

6. A process for preparing a compound according to Claim wherein Z is –N(OH)CHO, comprising the steps of:

a) converting a hydroxylamine of formula (2) into a compound of formula (1);



and thereafter if necessary:

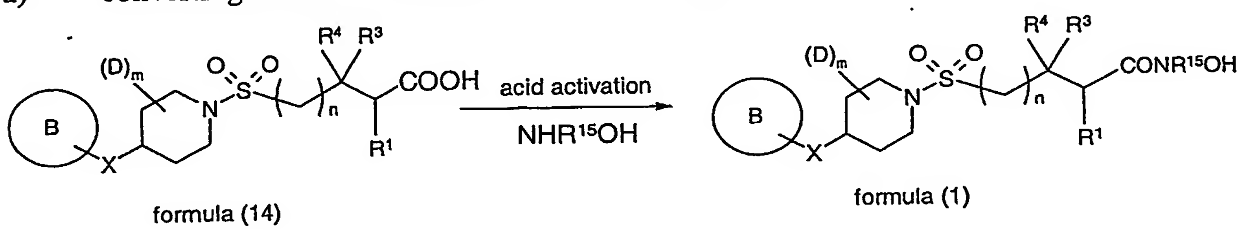
i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

7. A process for preparing a compound according to Claim 1 wherein Z is $-CONR^{15}OH$ comprising the steps of:

a) converting an acid of formula (14) into a compound of formula (1);



and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.